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Selected Rapporteur Summaries From the XX World Congress of Psychiatric Genetics, Hamburg, Germany, October 14–18, 2012

Heike Anderson-Schmidt,[1] Olga Beltcheva,[2] Mariko D. Brandon,[3] Enda M. Byrne,[4] Eric J. Diehl,[5] Laramie Duncan,[6] Suzanne D. Gonzalez,[7] Eilis Hannon,[8] Katri Kantojärvi,[9] Iordanis Karagiannidis,[10] Mark Z. Kos,[11] Eszter Kotyuk,[12] Benjamin I. Laufer,[5] Katarzyna Mantha,[5] Nathaniel W. McGregor,[13] Sandra Meier,[14] Vanessa Nieratschker,[15] Helen Spiers,[16] Alessio Squassina,[17] Geeta A. Thakur,[18] Yash Tiwari,[19] Biju Viswanath,[20] Michael J. Way,[21] Cybele C.P. Wong,[22] Anne O'Shea,[23] and Lynn E. DeLisi[23]*

[1]Section of Psychiatric Genetics, Department of Psychiatry and Psychotherapy, University Medical Centre Göttingen, Goettingen, Germany

[2]Molecular Medicine Center, Medical University—Sofia, SBALAG "Maichin dom", Bulgaria

[3]Meharry Medical College, Nashville, Tennessee

[4]The University of Queensland, Queensland Brain Institute, St. Lucia, QLD, Australia

[5]University of Western Ontario, London, Ontario, Canada

[6]Harvard School of Public Health, Boston, Massachusetts

[7]Texas Tech University Health Sciences Center, Center of Excellence in Neurosciences, San Antonio, Texas

[8]Institute of Psychologoical Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Heath Park, Cardiff

[9]Department of Medical Genetics, University of Helsinki, University of Helsinki, Helsinki, Finland

[10]Department of Molecular Biology and Genetics, Democritus University of Thrace, Panepistimioupoli, Dragana Alexandroupoli, Greece

[11]Texas Biomedical Research Institute, San Antonio, Texas

[12]Institute of Psychology, Eötvös Loránd University, Budapest, Hungary

[13]Faculty of Medicine and Health Sciences, Division of Biomedical Sciences, Department of Psychiatry, University of Stellenbosch, Tygerberg Medical Campus, Tygerberg, South Africa

[14]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health Mannheim, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

[15]Medical Faculty Mannheim, Heidelberg University, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany

[16]King's College London, MRC SGDP Centre PO82, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, United Kingdom

[17]Department of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari, Sestu-Monserrato, Cagliari, Italy

[18]Integrated Program in Neuroscience, McGill University, Douglas Mental Health University Institute, Montreal, Quebec, Canada

[19]Neuroscience Research Australia (NeuRA), Sydney, Australia

[20]Department of Psychiatry, National Institute of Mental Health and Neuro Sciences, Bangalore, India

[21]University College London, Molecular Psychiatry Laboratory, UCL Mental Health Sciences Unit, London, United Kingdom

All authors contributed equally to this work.

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*Correspondence to:
Dr. Lynn E. DeLisi, M.D., Harvard Medical School, Brockton VA Boston Healthcare System, 940 Belmont Street, Brockton, MA 02301.
E-mail: delisi76@aol.com

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[22]MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, P080, King's College London, London, United Kingdom
[23]Harvard Medical School, Brockton VA Boston Healthcare System, Brockton, Massachusetts

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The XXth World Congress of Psychiatric Genetics **(WCPG), sponsored by** ***The International Society of Psychiatric Genetics*** **(ISPG) took place in Hamburg, Germany on October 14–18, 2012. Approximately 600 participants gathered to discuss the latest findings in this rapidly advancing field. The following report was written by student travel awardees. Each was assigned sessions as rapporteurs. This manuscript represents topics covered in most, but not all, oral presentations during the conference, and some of the major notable new findings reported at this 2012 WCPG.**

Key words: International Society of Psychiatric Genetics; World Congress of Psychiatric Genetics; sequencing; DNA; SCZ; PTSD; substance abuse; pharmacogenomics

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INTRODUCTION

The XX World Congress of Psychiatric Genetics, sponsored by *The International Society of Psychiatric Genetics* took place October 14–18, 2012. Over 600 researchers gathered to discuss the latest technological advances in the field and new findings about the genetics of mental disorders.

The International Society of Psychiatric Genetics (ISPG) was first established as a non-proifit corporation in the USA in 1992 and is a worldwide organization that strives for the highest standards in the application of genetic methodologies to the study of psychiatric disorders. It was formed to provide a stable structure for continual congresses in this field with the mission of overseeing a rotating congress chairperson and program committee. This year the congress was co-chaired by Markus M. Nöthen (Bonn, Germany) and Marcella Rietschel (Mannheim, Germany). The following report represents topics covered during most oral sessions at this conference and several of the major findings presented. Rapporteurs for these sessions were student travel awardees who were assigned to summarize individual sessions and their discussions. Similar accounts of the 2007, 2008, 2009, 2010, and 2011 congresses held in New York City, Osaka, Japan, San Diego, California, Athens, Greece, and Washington, DC were previously published [Alkelai et al., 2008; Bergen et al., 2009, 2011; Amstadter et al., 2010; Dai et al., 2012].

Plenary Sessions (Reported by Olga Beltcheva, Geeta Thakur, Yash Tiwari, and Cybele C.P. Wong)

Professor Karl Zilles (Vogt Brain Research Institute, University of Düsseldorf) spoke on the architecture of the human brain and began by stating that complete brain modeling requires a multimodal approach from four important areas, that is, cytoarchitectonics—*brain histology*, receptor architectonics, [Zilles and Amunts, 2009], connectomics [Leergaard et al., 2012], and functional architectonics The first key issue he raised was that the more than 100 years old Brodmann brain map has drawbacks, as it lacks mapping information on two-third of the human cerebral cortex. The Brodmann model, did not study the intersubject variability of the boundaries and size of cortical areas [Amunts et al., 2000; Zilles and Amunts, 2010]. Brodmann boundaries were observer-dependent and do not match more recent functional and connectional magnetic resonance imaging (MRI) studies, which are observer-independent [Amunts and Zilles, 2001; Caspers et al., 2012]. This suggests a need for a more modern approach to brain anatomy which is statistically testable in identifying cytoarchitectural areas and mapping them to specific brain regions that could be transferred to MRI. Professor Zilles noted that JuBrain project (http://www.fz-juelich.de/inm/inm-1/EN/Forschung/JuBrain/_node.html) is the research initiative to develop a three-dimensional, realistic model of the human brain, focusing on continuous stereotaxic anatomical maps or probability maps of cortical areas. Probability maps are superior to schematic maps and currently available for more than 20 rat brains. Probability maps also helped to identify FP1 (Frontal Pole 1) and FP2 areas and the seven neocortical areas (Te 2.1–Te 7) of receptor architecture, that have not been identified in the cytoarchitectonical map of Brodmann [Zilles and Amunts, 2009]. Work related to Three-dimensional maximum probability maps, which are easier to understand, is in progress.

Professor Zilles then introduced the Human Brain Project (http://www.humanbrainproject.eu/) which integrates their current knowledge of brain into computer models, using these models to simulate the actual working of the brain. This work involving full brain coverage at 20 μm isotypic resolution is in progress. This project would allow researchers to locate single cells, capillaries, and layers of cortex. It would be possible to navigate and locate to any site of brain, compare its architecture, and reach far behind the resolution of MRI scanner. By giving an example of hippocampus structure, he explained why detailed cortical sub-divisions are essential for a meaningful anatomical and functional interpretation. These could then be correlated with genome data in order to understand the genetics of brain architectural variation.

The synchrony of different receptors in different brain regions decides brain function. An example he gave is the AMPA receptor (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) distribution in primary motor cortex and hippocampus CA1-3 [Zilles et al., 2004]. Rceptor fingerprinting [Palomero-Gallagher et al., 2008] can be valuable for computational models.

MRI technology has limitation in its resolution, for example in exAMINING 2 μm thick fibers. MRI also needs a lot of modeling and more modeling initially could provide more complex results. He discussed his studies with fiber tracts and concluded that diffusion tensor imaging (DTI) and connectomic studies are both supplementary and should not be treated as a replacement for each other. He displayed a video analyzing a fiber tract with ultra-high resolution polarized light imaging (PLI) in human striate cortex [Axer et al., 2011], and projected to the level of myelinated fiber with clear resolution. In summary, he noted that imaging began with a 1 cm resolution and currently can reach up to a 1 μm resolution, such that a single fiber can be seen, ultimately aiding in studying brain connectivity.

Dr. Mark Daly (Massachusetts General Hospital) reviewed the genetic architecture of psychiatric disorders and highlighted what he felt were the breakthroughs in genetic studies of psychiatric disorders. During the ''dark ages,'' those in the field faced the paradox that despite the clear heritable nature of these disorders, candidate gene and linkage studies were failing to substantiate this, although a model of many genes with incomplete penetrance could easily explain this paradox. He identified the three key aspects of the recent successes of psychiatric genetics; technology, collaboration, and genome resources. He discussed the increased burden of copy number variants (CNVs) in psychiatric disorders, and implicated specific loci, many of which have since been associated with multiple psychiatric disorders. However despite many regions with CNVs being identified, extracting genes and treatment targets is a slow process.

In the search for common variants through genome wide association studies (GWAS), unfruitful initial attempts led some researchers to conclude that common variants were not the answer, and declared that rare variants were the way forward. The work of Shaun Purcell, however, provided proof of a polygenic model for common variants [Purcell et al., 2009]. Similar to the CNV story, this suggested persisting with GWAS would ultimately yield results. Through collaboration, in particular the Psychiatric GWAS Consortium (PGC), substantial breakthroughs were made last year for Schizophrenia (SCZ) [Ripke et al., 2011]. Dr. Daly presented a table he produced in 2011 of the number of hits per magnitude of sample size increase for SCZ, comparing it to progress seen in other conditions, such as Crohn's disease and height. Continued addition tripled the sample size of the PGC, bringing a further jump forward that identified 62 genome-wide significant regions for SCZ and put it on a trajectory similar to that of other complex traits. Other psychiatric disorders are still lagging behind in sample size, so it remains to be seen if a similar number of associations will be found with equivalent sample size increases in other disorders, particularly for childhood disorders.

He commented on the potential of next generation sequencing for understanding human disease, but there are still difficulties facing studies of rare variants. In particular, the high proportion of neutral variants complicates the detection of true disease effects. Current studies for autism and SCZ are comparable to initial GWAS studies, with little deviating from the null distribution. Extrapolating from the PGC GWAS, he stated that power is greatly reduced at lower allele frequencies, citing that a common variant of small effect (odds ratio (OR) = 1.2) is approximately equal to a rare variant (frequency 0.5%) with an OR of 3. Finally, he briefly considered de novo mutations and presented observations from an initial study of autism trios, stating that de novo mutations contribute little to overall disease risk with only 10–20% of autism cases having a relevant de novo mutation. He concluded by stating that despite GWAS explaining little of the disease variance, they will yield substantial biological insights and emphasized the continual need for larger sample sizes.

Dr. Bryan Roth (University of North Carolina Chapel Hill Medical School) discussed ''Novel Approaches to Psychiatric Drug Discovery.'' As an introduction, he pointed out that now, when the human genome is sequenced, we possess the tools to evaluate every possible ''druggable target'' and receptors are among the best candidates. The Roth team has been working on class A G-coupled protein receptors (GPCR), numbering approximately 300 members, which at present are targeted by only a small number of drugs. They have developed and validated a highly automated pipeline, which allows them to perform parallel screening of hundreds of targets. As an example of the possible applications for this platform, Dr. Roth presented his on-going work on the hallucinogenic compound Salvinorin A. They screened the drug against a large library of central nervous system molecular target and found that it is unique in having an absolute selectivity for a single target, the opioid receptor [Roth et al., 2002]. Determining the mode of interaction between ligand and receptor became possible only after the structure of this GPCR was solved in collaboration with Ray Stevens, The Scripps Research Institute [Thompson et al., 2012]. It appears that Salvinorin A binds the helical bundle of the receptor, engaging primarily non-conserved residues. Since it is uncharged, it does not interact with a highly conserved aspartic acid residue, found in all opioid and biogenic amine receptors, which is known to bind the positively charged amine groups of the ligands. At present, Dr. Roth's team continues working on the biochemical effects on the cell following the binding of the compound to the opioid receptor. He concluded that the ultimate goal of psychiatric genetics is to have a finding that will help the development of a cure, rather than just treatment of rare and common diseases. There are several problems which need to be approached in order to achieve that: first, the ''single target problem,'' where the disorder is due to rare catastrophic mutation (s); second, the ''multi-target problem,'' where the disease results from multiple variants each with modest effect; and third, the problem of those disorders for which there are no known druggable targets.

As more human genomes are sequenced more catastrophic mutations will be found. Usually they will affect only a limited number of individuals, so the most practical approach for drug development would be to repurpose approved drugs, instead of developing completely novel compounds. As an example for that approach Dr. Roth presented work on Angelman syndrome—a neurodevelopmental disorder, resulting from inactivation of the

gene for ubiquitin protein ligase E3A (UBE3A) on the maternal chromosome in neurons [Huang et al., 2011]. They attempted to identify molecule(s), which could activate the healthy silenced copy of the gene, using the automated pipline. Embryonic neuronal cell lines from knock-in animals with a deletion of the maternal allele were screened using a library enriched in FDA approved and EU approved drugs as well as drugs which have been used in human. One compound, irinotecan—a topoisomerase inhibitor used for cancer treatment, managed to unsilence UBE3A. Its in vivo testing is still underway. Using a similar approach Dr. Roth's lab is currently working on other diseases, such as Rett and Prader-Willi syndromes. The first results from these projects are expected within a year.

A completely different situation can be seen in the field of drug development for SCZ. To this date the majority of compounds directed towards receptors involved in this disease have turned out to be ineffective. It is highly possible that every future drug developed following the current concepts would probably be unsuccessful because we are dealing with a complex disease, which cannot be treated with a single target agent. In order to address that, his team is currently working on the multi target design problem prospectively by creating drugs in silico in collaboration with Andrew Hopkins, Dundeee University. Dr. Roth's team is also trying to tackle the problem with SCZ drug discovery using the principle of functional selectivity. They have based their work on the hypothesis that the single target drugs simply bias the receptor by forcing it to adapt certain conformations. Thus, one could argue that for example the canonical, G-protein mediated, GPCR pathway is responsible for the side effects of these drugs, while signaling through the non-canonical, arrestin mediated pathway, accounts for its therapeutic actions. Dr. Roth's team has tested the hypothesis by attempting to develop ligands of D2 dopamine receptors which affect only arrestin signaling [Allen et al., 2011; Chen et al., 2012]. The goal was to create a compound, which was inactive on the canonical and highly active on the non-canonical pathway. They created a library of synthetic analogs of aripiprazole, a well known and widely used antipsychotic drug, with the help of a directed medicinal chemistry approach and tested them with the parallel screening pipeline. They found three molecules, which have no activity on the canonical G protein signaling, but are effectively blocking arrestin signaling. This ligand-receptor effect has been confirmed in arrestin knock-out mice. The new compounds have good pharmacokinetics and readily pass the blood–brain barrier. The initial data show that they have no motoric side effect unlike other compounds used for treatment of SCZ. At present the aripiprazole analogs have now advanced towards in vivo testing.

Dr. Peter Visscher (University of Queensland) spoke on "the missing heritability in psychiatric genetics." He briefly defined heritability as the proportion of phenotypic variation that is due to genetic factors. It is a population-specific parameter that can be estimated without knowing the information of individual genes. The estimation of heritability depends on the scale of measurement. In a dichotomous disease risk scale, heritability estimates are dependent on prevalence of disease. Alternatively, heritability can be estimated via burden/liability model, in which the risk of disease that is due to multiple genetic and environmental factors can be expressed on a continuous scale. The burden/liability models give predictions that are consistent with (a) the observed recurrence risk of relatives in SCZ in the McGue et al. [1983] and Lichtenstein et al. [2009] studies, suggesting a strong additive genetic effect of disease risk; (b) the idea that sporadic cases are normally found in complex diseases as demonstrated in [Yang et al., 2010]; and (c) the high discordance of heritability of liability observed in monozygotic twins due to the use of simple models [Smith, 1970].

The estimated heritability of disorders can also be limited by the selection of a population. For example, the heritability estimates of SCZ is 0.81 in a twin population (meta-analysis performed by Sullivan et al. [2003] and 0.64 in the Swedish National study [Lichtenstein et al., 2009]. The combination of allele frequency and effect size of risk loci determines their contribution to heritability of disorders. Data from the PGC1-SCZ study showed both the extremely rare 22q11 deletion (effect size >20) and ZNF804A (effect size $= 1.1$, risk allele frequency $= 0.59$) explain $\sim$0.1% variation in liability in SCZ. Variants with low frequency (0.001–0.01) and intermediate penetrance [described by Sullivan et al.'s, 2012 model of genetic architecture] has remained underrepresented in current literature. The additional 62 SNPs identified from the PGC2 GWAS will hopefully fill in the gap of missing heritability.

It is known that siblings do not share exactly 50% genes from their parents due to segregation and recombination of loci [heritability estimates $= 0.31$–0.64, SD $= 0.04$; Visscher et al., 2006]. In contrast to the misunderstanding that new variants introduce missing heritability, Dr. Visscher pointed out that de novo variants arise across generations and can potentially lead to the increase of heritability by 0.001–0.01%. More evidence is expecting to emerge in the next few years. Other reasons such as chip design, statistical power as well as interactions among the variants and environment can explain missing heritability. Yang et al.'s [2011] study on human height has provided a direct estimation of missing heritability in GWAS. The variation of human height captured by all common SNPs is 40–50% and it has now been referred to as "chip heritability." In SCZ, the "chip heritability" ranges from 23% to 34% [Lee et al., 2012]. The narrow sense of heritability captured by GWAS is likely due to the absence of low frequency variants that are not in linkage disequilibrium with the common SNPs. Dr. Visscher quoted "Essentially, all models are wrong, but some are useful" from George E.P. Box (c.1919) to conclude his talk. The liability composed of environmental factors, segregating and de novo variants will explain phenotypic heterogeneity and the heritability of disorders.

This year, Dr. Raymond Crowe, Professor Emeritus from the University of Iowa, USA, was awarded the Snow and Ming Tsuang Lifetime Achievement Award. In his talk, he journeyed through his professional career path of nearly 45 years and reviewed how the field of psychiatric genetics has evolved over the years, mentioning some key players at Iowa. Although formally trained as a medical doctor, his genetic career began the day he met Dr. Leonard Heston (Iowa City, USA) and was inspired by the adoption studies of SCZ, which changed attitudes towards causation of mental illness. Dr. Crowe's early career in the 1970s started with his first publication in 1972 entitled "The Adopted Offspring of Women Criminal Offenders" and "An Adoption Study of Antisocial Personality" in 1974.

Dr. Crowe shared memories of working at Iowa when there was no genotyping lab. In the fall of 1984, he did the 1st DNA genotyping in the basement of the psychiatry department and it took 1 week. Dr. Crowe is a pioneer in studies of panic disorder and published the first linkage paper of panic disorder in 1987. Dr. Crowe also spoke about his involvement in the ''Iowa 500 study'' where voluminous and extensive details were collected to make diagnostic criteria which influenced the DSM. The ''Iowa 500'' was a majore contributer to progress in psychiatric genetics as current studies of patients and families still employ the methodology they introduced in the 1970s. He also mentioned the Collaborative Study on the Genetics of Alcoholism (COGA) which was designed in the 1980s. Multiplex pedigrees with alcoholism were collected and this study has stood the test of time with a design that is still yielding good results today. Dr. Crowe quoted Charles Dickens saying: ''It was the best of time; it was the worst of times.'' He was reminiscent of how many things have been learned about psychiatric disorders over the years, such as how diseases are being transmitted, about the polygenic model and notion of complex inheritance, and how the field of psychiatric genetics has so many layers of complexity. He concluded with a modified quote from his own medical doctor: ''Half of what we believe is wrong and the other half of what we know is not what we would expect.''

Affective and Anxiety Disorders (Reported by Enda Byrne, Nathaniel McGregor, and Alessio Squassina)

Bipolar disorder (BP). Dr. Elaine Green (Cardiff University, UK) reported on findings from the genotyping of 2,106 SNPs, selected from the Ferreira et al. [2008] meta-analysis in a sample of 1,218 BD patients and 2,913 healthy controls. CACNA1C and ODZ4 genes as well as region 15q14 were replicated, but not the ANK3 gene. Two significant SNPs were located in regions not previously associated with BD (12q13.1 and an intronic SNP in the TRPC4AP gene, Ch. 20q11.2).

Dr. George Kirov (Cardiff University, UK) discussed new data from a study on de novo CNVs carried out on a sample of 282 BD and 76 SCZ families. Thirteen CNVs were identified in 302 BD offspring (4.3% rate) and six in the SCZ sample (rate 7.9%). These rates were significantly higher than in healthy controls (rate 1–2%). The median size of de novo CNVs was 160 Kb in BD and 640 Kb in SZ.

Dr. Nirmala Akula (NIMH, USA) presented findings from the first RNA sequencing study in BD performed postmortem on dorsolateral prefrontal cortex from two different samples comprising 11 BD subjects and 11 controls. PROM1, ABCG2, A2M and FLI1 genes as well as the long non-coding RNA, LINC00173, were dysregulated in BD. Of the several GO categories functionally enriched, ''ion binding'' and ''neuronal development'' were also enriched for GWAS signals. Many genes were replicated by microarrays in an independent sample of 22 cases and 26 controls.

Dr. Stéphane Jamain (Inserm, France) resequenced the promoter and regulatory regions of the ASMT gene (involved in melatonin metabolism) in 345 BD patients and 220 controls [Etain et al., 2012] identifying eight rare variants associated with BD and reduced enzymatic activity. A common variant (SNP rs4446909) was also associated with BD and with lower mRNA level and enzymatic activity. Findings were replicated in an independent cohort (480 BD patients and 672 controls) and in the combination of both datasets.

Dr. Thomas Schulze (University of Göttingen, Germany) spoke on behalf of Dr. Rene Breuer (Central Institute of Mental Health, Germany). Using a market research tool (association rule mining), the study searched for associations between genotypes of SNPs selected from a previously published GWAS on BD [McMahon et al., 2010] and multiple phenotypes in a sample of 2,835 BD patients and 2,744 controls (comprising a discovery and a replication sample). One multilocus genotype pattern was associated with comorbid eating disorders (combined $P = 4.937E{-}14$, $OR = 4.1$) and another one was associated with simple phobia (combined $P = 1.686E{-}11$, $OR = 3.2$).

Dr. Pamela Sklar (Mount Sinai School of Medicine, USA) presented findings from a PGC-BD GWAS study on 25,000 subjects performed by using different platforms for detecting both rare and common variants. Analyses revealed a number of significant SNPs located in CACNA1C, ODZ4, CAPN10, TRANK1, LMAN2L, and VIPR2 genes. Some of these genes were previously implicated in BD by GWAS while others are correlated with pathways previously involved.

Depression. Dr. Elisabeth Binder emphasized the role of environment in depression, the need to increase focus on the environment, and the need for better identification of relevant environmental variables. She highlighted that biological systems that mediate response to the environment could be important and that the stress hormone system is known to be disrupted in stress-related disorders. A key molecule for regulating stress response is the glucocorticoid receptor. A cohort of 160 males were treated with a glucocorticoid-receptor agonist and their gene expression was measured prior to treatment and 3 hr later. QTLs that were associated with altered gene expression were identified. SNPs were enriched in glucocorticoid response elements and glucocorticoid receptor-associated transcription factors. Furthermore, these SNPs show more evidence of association with Major Depressive Disorder (MDD) than random selections of SNPs. There was some evidence that the QTLs acted by altering long-range chromatin interactions. This study provided direct evidence for a gene $\times$ environment interaction at the molecular biological level.

Dr. Robert Power (Kings College London) presented a study on the evolutionary consequences of depression alleles on fitness. Fitness was measured by fecundity. Prior evidence suggests that there is no decrease in fecundity in MDD cases and siblings of cases have more children on average. Using data from the Swedish population registry, genetic profile scores were constructed for $>2{,}500$ individuals using the results from the Psychiatric Genomics Consortium MDD GWAS, and regressed on the number of grandchildren each individual had. An inverted u-shaped distribution was found, with those carrying an average number of depression alleles found to have the most grandchildren, and those carrying either more depression alleles or fewer depression alleles than average had fewer grandchildren. A study on the effects of inbreeding on depression risk was presented. Using data from the PGC MDD study, runs of homozygosity (ROH) were identified and a test for excess of ROH was performed. No consistent pattern was found between cohorts.

Dr. Sarah Mostafaci (Stanford University) presented a study that combined pathways and RNA-sequencing expression data to unravel the functional units that contribute to MDD. Analysis of gene expression patterns found in cases and not in controls may help to identify biological markers that are informative of the pathophysiology of MDD. Gene expression was measured in 459 recurrent cases and 463 controls. The participants had also been genotyped on a GWAS chip. After extensive QC, QTLs were identified and gene-wise statistics were computed. Two significant pathways were identified. These pathways were related to cell migration through the cytoskeleton and cell adhesion, respectively. All QTLs for genes in the significant pathways were identified and tested for association with MDD. Nine SNPs were significant.

Dr. Gerome Breen (King's College London) highlighted the lack of significant findings in GWAS studies of MDD. This could be due to many factors, foremost amongst them, the need for larger sample sizes. He presented data showing that a GWS significant hit had been identified in an analysis of late-onset depression, but replication has not yet been attempted. Furthermore, he highlighted that early-onset recurrent depression had a higher heritability and that focusing on depression subtypes may be informative. CNVs have not been widely investigated in MDD, but there is evidence for an excess of exonic deletions in cases compared to controls. Epigenetics is another area that offers promise for future investigations of MDD.

Dr. Cathryn Lewis (King's College London, UK) discussed the failure of genome-wide association studies to identify replicable risk alleles for MDD. She indicated that her group believes that heterogeneity may be providing sufficient noise to reduce power, preventing association from being detected, but that looking at age at onset (AAO) in the PGC-MDD data could reduce some of the heterogenic noise observed. She discussed her approach of using octiles of AAO distribution within each study, due to an assumption that heterogeneity around AAO was a result of study-specific differences and not differences in depression cases. AAO was found to differ significantly by study with medians ranging from 20 to 37 years of age. The majority of depression cases were found to be below 40 years of age. With this strategy one single nucleotide polymorphism (SNP) was found to be in full genome-wide association in the PGC-MDD cohort and a number of other SNPs showed "suggestive significance." Dr. Lewis showed that AAO can be considered a usual covariate tool for reducing the heterogeneity of depression in the analysis of data across studies, although this still proves to be challenging due to cross-study differences.

Karen Hodgson (King's College London, UK) discussed genetic predictors of antidepressant side effects. In order to assess which patients are at greater risk for developing a particular drug-related side-effect, adverse drug reactions were categorized into one of four groupings, namely adrenergic, cholinergic, serotonergic, and histaminergic. A patient cohort ranging from moderately to severely depressed patients was used with the drug focus being escitalopram (an SSRI) and nortriptyline (a TCA). Genetic prediction association was found only for the serotonergic group, namely rs6644093 ($P = 7.43 \times 10^{-5}$) in *HTR-2C*. No significant association was found in the remaining three adverse reactions groupings, but this was postulated to be due to reduced power as a result of low sample numbers within drug-specific groupings.

Anxiety disorders. A common underlying diathesis amongst anxiety disorders was presented by Dr. John Hettema (Virginia Commonwealth University, USA). He presented work pertaining to the integration of data across multiple anxiety disorders for input into GWAS to find possible common underlying associations. Target cohorts for analysis comprised panic disorder, generalized anxiety disorder and several phobic disorder categories for six European ancestry samples totalling 24,000 individuals. GWAS meta-analysis showed nominal association for several prior candidate genes but further analysis is still currently underway.

TMEM132D had been implicated by many an independent study in the pathogenesis of anxiety disorder. Last year Erhardt and colleagues identified TMEM132D as a potential candidate gene for panic disorder [Erhardt et al., 2011]. Dr. Angelika Erhardt (Max-Planck Institute, Germany) spoke about methylation patterns within the *TMEM132D* gene. Professor Erhardt looked at 116 CpG sites in DNA extracted from peripheral blood in traumatized individuals from the inner city of Atlanta. She found no associated between panic risk variants and *TMEM132D* methylation but did find association between methylation patterns and PSS scores for anxiety. She also alluded to a lower pattern of methylation being associated with post-traumatic stress disorder (PTSD).

Dr. Martin Kohli studied repeat expansions within the *C9ORF72* gene and its contribution towards Alzheimer's disease (AZ). Dr. Kohli's presented findings alluded that the expansion repeat in C90RF72 (>30 expansions) can contribute to the pathogenicity of AZ, in addition to its current association with frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). The repeat is also less frequent in African than European Americans (EAs), and this points to differences in ancestral haplotype frequencies, including haplotypes at potentially different risks for repeat expansion.

Schizophrenia (SCZ; Reported by Mark Z. Kos, Sandra Meier, and Heike Anderson-Schmidt)

Yi Lin (University College, London, UK) studied missense mutations in *CACNG5* and its association with SCZ and BP. She discussed her work which aimed to identify disease relevant genetic variation in the calcium channel gene *CACNG5* and study it's possibly biological implications in vitro. Yi found an association of the rs17645023 marker in a case versus case analysis ($P = 6.3 \times 10^{-7}$) and also in a combined analysis of eight non-synonymous SNPs in the *CACNG5* gene in SCZ and bipolar patients versus controls ($P = 0.00082$), bringing the session to a very positive close.

Dr. Aiden Corvin (Trinity College Dublin, Ireland) investigated whether protein-activated kinase 7 (PAK7) duplications in an Irish sample of SCZ patients, were generalizable to other psychotic disorders and whether this represented a rare regional duplication. PAK7 duplications were found to be more generally associated with psychosis and not just SCZ. However, this particular duplication appears to be more frequent in Ireland and the UK, suggesting a common ancestral mutated event. Close relatedness within the samples was tested and eliminated as a possibile explanation for these results. PAK7 mutations have clinincal implications as the majority (12 out of 13) of mutation carriers had a chronic course of illness and poor outcome. The exact genetic mechanisms of PAK7

are yet to be determined. However, similar to DISC1, this gene appears to be involved in dentritic spine regulation [Brandon and Sawa, 2011]. It was discussed that this mutation might also be present in underpowered samples of other European ancestries.

Dr. Linh Duong (Institute of Biological Psychiatry, Copenhagen University Hospital, Roskilde, Denmark) presented a detailed genetic analysis of two patients and their families on the Neuroxin1-Gene (NRXN1) to investigate possible gene-specific psychopathological phenotypes. NRXN1 has previously been implicated in SCZ, autism spectrum disorders, and intellectual disability [Shah et al., 2010]. Both patients had early onsets of mental difficulties and low social functioning. Patient 1 was diagnosed with autism, mental retardation, and epilepsy whereas patient two fulfilled the criteria for SCZ. Genotyping revealed that patient 1 carried a large CNV deletion (451 kb), in addition to a point mutation. Patient 1 showed a family history of autism (maternally) and SCZ (paternally). In contrast, patient 2 had two closely linked small CNVs and while there was some family history (schizophreniform disorder, depression), not all mutation carriers were affected. Dr. Duong's study [Duong et al., 2012] illustrates the diverse clinical manifestations (type and severity) resulting from NRXN1 mutations, implying pleiotropy and incomplete penetrance in NRXN1. The severity of the disease was not correlated with any one mutation.

Ms. de Candia (University of Colorado, Boulder, USA) investigated whether specific SNPs, linked with SCZ, are shared across populations or are population-specific. To date, most genetic analyses are carried out on people of European descent. Few direct comparisons between SCZ patients of different ethnicities exist. De Candia examined the extent to which additive genetic variance in susceptibility to SCZ is shared by people of EA and African American (AA). A genotypic similarity score was computed based on an established method [Yang et al., 2012]. Controlling for confounds, it was found that common SNPs predict a large proportion of the genetic variance in both populations. While there was evidence for shared genetic variance, the samples were not pure but consisted of mixed populations particularly within the AA group. In addition, environmental effects were not taken into consideration.

Dr. Ruderfer (Mount Sinai School of Medicine, New York, NY, USA) examined the role rare recessive heterozygote variants play in SCZ based on the rationale that for every 1% increase in autozygosity the odds of developing SCZ increase by 17% [Keller et al., 2011]. It was found that patients with SCZ did not show a significant increase in rare loss of function (LOF) variants of any particular gene. ROH suggest autozygous regions that are enriched for recessive mutations. However, no different rates were found for cases and controls.

Dr. O'Dushlaine (The Broad Institute, Cambridge, USA) used the lobSTR algorithm [Gymrek et al., 2012] to assess tandem repeat variations in 5,000 SCZ exomes in a Swedish sample. This was based on the rationale that no comprehensive survey of exome repeat variations in SCZ had been carried out to date. Contrary to expectations, no evidence was found for an overall significantly increased burden of repeat variations in cases compared to controls. However, specific local variants were enriched in patients with SCZ highlighting potential new candidates for SCZ susceptibility. Various different small and non-frameshifting events at these loci might thus increase the risk for SCZ.

Dr. Degenhardt (Institute of Human Genetics, University of Bonn, Germany), presented her results based on an analysis of CNVs in genes that have previously been reported to carry de novo mutations in SCZ [Girard et al., 2011; Xu et al., 2011]. Fifty-five candidate genes were therefore screened for CNVs in populations of cases (SCZ and schizoaffective) and controls. Higher rates of RB1CC1 duplications were found in 7,500 patients with SCZ compared to 112,000 controls, illustrating the success of a candidate gene approach. RB1CC1 has previously been found in children with intellectual disability [Cooper et al., 2011] and appears to be related to cognitive impairments.

Dr. Colm O'Dushlaine (Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Boston, MA, USA) presented the results from a large genome-wide association study (GWAS) combining the data of the 1.wave of the PGC workgroup SCZ with a Swedish sample. The Swedish cohort was ascertained via electronic hospital records, all patients were assigned a clinical diagnosis of SCZ and both of their parents were of Swedish ancestry. In sum the Swedish sample included 5,351 cases and 6,509 control subjects. The sample was very homogeneous, only a few Finnish outliers could be observed in multidimensional scaling plots. Six percent of the variance in the Swedish was explained by the polygenic score of PGC 1.wave sample. The GWAS revealed novel genome-wide significant associations at *C2orf69* and *SNX19*. One hundred fifty-four of 201 SNPs displayed the same direction of effect in the Swedish cohort as in the PGC 1.wave sample (sign test $P = 8 \times 10^{-15}$). Additionally, the results increased the evidence for a *MIR137* association and deletions at 9q21.11 and 22q11.21, as well as duplications at 16p11.2, 11p11.21, and 7q36.1.

Dr. Stephan Ripke (Center for Human Genetic Research, Broad Institute of MIT and Harvard, Boston, MA, USA) reported the results of a GWAS including the data of the 1.wave of the PGC SCZ and BP workgroups. Genome-wide significant was observed at *PIK3C2A* and *ELTD1*. Dr. Ripke noted the problem of overlapping control samples and matching procedure for bipolar and SCZ patients. Surprisingly no locus surpassed the threshold of genome-wide significance in the comparison of these two phenotypes. Additionally the polygenic score of PGC 1.wave bipolar sample significantly predicted the mania subphenotype of SCZ ($P = 0.005$), but not those of depression, negative, and positive symptoms.

Dr. Robert Power (Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, London, UK) discussed the false discovery rate (FDR) procedure. This is designed to control the expected proportion of incorrectly rejected *null hypotheses*. He suggested that the FDR performs better in finding non-null SNPs. Further he proposed that a FDR procedure conditioned on comorbidities in SCZ would lead to smaller FDR values for a given effect size, which might empower analyses.

Dr. Anders BØrglum reported on a GWAS of 915 SCZ patients and 915 matched control subjects, with initial results followed up in Danish, German and Dutch samples. No marker surpassed the threshold of genome-wide significance (best *P* values at *RUNDC2A* ($P = 9.04 \times 10^{-7}$) and *CDH13* (1.2×10^{-6})), region-based analysis revealed a significant association of *ZEB1*, which was successfully replicated. *ZEB1* is regulated by *TCF4* and is involved in the regulation of *CDH13*. Dr. BØrglum further presented the results from a genome-wide interaction analysis, which revealed that

genetic variation at *CTNNA3* in interaction with maternal cytomegalovirus infection increased susceptibility to SCZ.

Dr. Giulio Genovese (Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Boston, MA, USA) refered to missing pieces of the human genome (megabase pairs of euchromatic human genome sequence that have no home on the reference human genome assembly). He described an approach for localizing these missing pieces utilizing the patterns of genome sequence variation created by population admixture. He observed that most of the hereby identified sequences were hidden in the genome's heterochromatic regions. One region harboring such missing pieces is the 1q21.1 region. The 1q21.1 microdeletion has been reported to be associated with several clinical phenotypes. Several localized missing pieces mapped to the distal part of 1q21.1 and *HYDIN2*.

Dr. Benjamin Neale (Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Boston, MA, USA) eported on a recent exome sequencing study of 13,000 individuals from the Swedish SCZ cohort, of these subjects 9,000 were clearly of European ancestry, 2,000 of African and 500 of Asian/Hispanic Ancestry. 1,107,051 nonsynonymous, 44,529 splice variants and 31,003 stop gain/loss variants were analysed with the Exome Chip. This chip further includes GWAS Tag SNPs, SNPs covering the HLA system and some common variants enabling to infer population stratification. The analyses of the rare variants resulted in no genome-wide significant association.

Dr. Ann Collins (University of North Carolina, Chapel Hill, NC, USA), discussed the potential role of *MIR137* (microRNA 137), a known regulator of neuronal development [Silber et al., 2008; Smrt et al., 2010; Szulwach et al., 2010] implicated in SCZ risk by PGC-1 [Ripke et al., 2011]. Focusing on an extensive linkage disequilibrium (LD) block comprised of top GWAS hits, the authors identified a haplotype with a significant, protective effect.

Dr. James Walters (Cardiff University, Cardiff, UK), presented the clinical and genetic validation of a new SCZ sample (CLOZUK; $n = 6{,}268$), collected anonymously from blood stored by the UK Human Tissue Authority and receiving treatment with clozapine, an antipsychotic for treatment-resistant SCZ. This unconventional sample was clinically validated, producing a positive predictive value (PPV) of 88% for narrow SCZ. Genetically, CLOZUK compares favorably with the PGC-1 findings, with 47% of the top PGC-1 hits ($n = 81$) showing nominally significant association in CLOZUK.

Dr. Olli Pietiläinen (Wellcome Trust Sanger Institute, Cambridge, UK) presented results of a genetic investigation of a Finnish population isolate with a high incidence of SCZ. Scanning their sample ($n = 173$) for deletions greater than 20 kb, they identified a rare, yet significantly enriched, deletion at 22q11.22. This deletion shows significant association with SCZ within the isolate ($P = 0.031$), as well as more broadly in the Finnish population ($P = 0.0065$), and appears to down-regulate the gene *TOP3B*.

Alex Richards (Cardiff University, Cardiff, UK). Spoke on the CLOZUK cohort, along with 475 Welsh samples with cognitive data. These were genotyped and tested for association with SCZ and cognitive performance. With the exception of *MHC* variants, none of the SNPs ($n \sim 200{,}000$) exhibited genome-wide significance. When meta-analyzed with the PGC-1 [Ripke et al., 2011], a number of top hits were successfully replicated, along with four new SNPs that attained genome-wide significance.

Eilis Hannon (Cardiff University, Cardiff, UK), discussed her group's analysis of gene expression patterns in fetal brains and their relationship to GWAS data for SCZ and BP. Using global transcriptome data for 13 brain regions from two independent studies [Johnson et al., 2009; Kang et al., 2011], they found genes with consistent expression across the mid-fetal brain to be enriched in both disorders.

Dr. Stephan Ripke (Center for Human Genetic Research and the Broad Institute, Boston, Massachusetts, USA and the PGC) spoke about the PGC, which is an international group of researchers aiming to maximize the utility of extant psychiatric GWAS through mega-analysis. Previously having identified multiple loci involved in SCZ using 20,000 individuals [Ripke et al., 2011], Dr. Ripke sought to increase the sample size to 25,000 cases and 28,000 controls for a collaborative analysis that includes samples from the UK, Sweden, and USA. This new combined meta-analysis has identified 62 SNPs with genome-wide significance in SCZ. Dr. Ripke reasoned that there may be an upper limit to the number of genes affected in this disorder. However, based on polygene modeling, he believes that a plateau has not yet been reached.

Dr. Menachem Fromer (Mount Sinai School of Medicine, New York, USA) reported on the role of integrating genetic variation with protein annotations in SCZ sequencing. He discussed whether protein domains might play a role in coding genetic variation, and whether this genetic variation contributes to disease risk. Dr. Fromer used exome sequencing from the 600 trios project from Bulgaria and from 2,500 cases and 2,500 controls in a study from Sweden using a combination of exome capture arrays, and applied InterProScan to annotate RefSeq gene transcripts with the location of their functional protein signatures. Dr. Fromer also used similarity matrix of proteins (SIMAP) [Rattei et al., 2010] to predict protein function and analyzed the data using PLINK/SEQ software. Analysis of variants will focus on de novo (rare) mutations including single nucleotide variants (SNVs), indels and CNVs [Fromer et al., 2012].

Dr. Panos Roussos (Mount Sinai School of Medicine, New York, USA) reported on gene coexpression networks, or integrative "omics," to examine gene networks for their enrichment for SCZ associated genetic risk variants. Transcriptome profiling of human post-mortem non-disease samples was used to explore modules of genes that may be risk factors for SCZ. Initially, an expression quantitative trait loci (eQTL) analysis was completed to examine whether common SCZ GWAS risk variants are enriched for eQTLs [Roussos et al., 2012]. Dr. Roussos also compiled a list of large risk factor CNVs from the literature and used de novo missense, nonsense, and splice site mutations obtained from exome sequencing. Using integrative "omics," he examined whether there was a gain or loss in the module connectivity in SCZ using two independent microarray datasets. Forty-six modules (52–1,792 nodes) were detected. He found that GWAS SCZ risk modules were enriched for genetic risk variants (eQTL, de novo mutations and CNVs) that disturbed critical hub genes in the modules.

Autism (Reported by Eric Diehl)

Dr. Scott Selleck (Pennsylvania State University, USA) discussed findings from assessing CNV burden in Autism Spectrum Disorder (ASD) cases. Using individuals from the Childhood Autism Risks from the Genetics and Environment (CHARGE) study [Hertz-Picciotto et al., 2006], the authors examined CNV burden in 107 genomic regions flanked by segmental duplications (genomic hotspots) as well as other rearrangement-prone areas. They found significantly more base pair duplications in ASD individuals versus controls, similar to previous work [Girirajan et al., 2011]. There was an increase in duplication burden in five specific hotspots. The results suggest a mechanistic bias toward duplications in the etiology of ASD.

Holly Cukier (Hussman Institute for Human Genetics, University of Miami, USA) presented findings from work related to exome sequencing in a large extended families which contain at least one pair of affected cousins. The authors hypothesized that dominant, partially penetrant variants would segregate with the pedigrees. By combining their exome data with available identity by decent (IBD) information, the authors were able to drastically filter potential regions harboring potential ASD related-variants. They identified mostly dominant changes, with some recessive and X-linked. They found 112 candidate genes in IBD regions. The genes identified included 13 known ASD gene and approximately a dozen novels genes, several recurrent in families. The authors conclude that use of IBD regions is robust for filtering, and can identify both novel and known diseases genes.

Anthony J. Griswold (Hussman Institute for Human Genetics, University of Miami, USA) presented research related to use of target sequencing of regions identified in ASD by GWAS. Dr. Griswold argued that targeted can be more effective than exome sequencing for identifying disease genes in genomic regions of interest. Using 919 unrelated cases with ASD and 854 controls, they targeted 689 genes plus 5 kb from their transcriptional starts and ends, conserved regions within non-genic haplotype blocks and entire haplotype blocks. Out of a total of 603,124 identified single nucleotide variants (SNVs) across all individuals, 48,891 (8.1%) occurred within exons or at splice junctions of one of the targeted genes, 15,099 (2.5%) induced nonsynonymous amino acid changes, and 8,829 (1.5%) were predicted to induce a damaging amino acid change. In the future, they plan to look at non-coding and intergenic variants as well as increasing sample size.

Christine M. Freitag (Goethe-University, Frankfurt, Germany) presented work related *Cntnap2*, a well-studied candidate gene in ASD. *Cntnap2* has appeared in many linkage, CNV, and association studies [Penagarikano and Geschwind, 2012]. It is expressed in ASD relevant brain regions related to speech, it also interacts with FOXP2. Thus far, no studies have examined promoter variants of *Cntnap2*. The authors hypothesized that promoter variants would be associated with ASD, that they would affect gene expression, and that they would influence language development. Using direct sequencing of 200 families, they identified 3 of the 10 annotated SNPs in the region, and seven novel SNPs in their sample group. There was a nominal association of the SNP rs34712024 and the short tandem repeat (STR) rs71781329 with ASD. The SNP rs150447075 was nominally associated with age of first sentence in months. rs34712024 and rs71781329 but not rs150447075 showed significant increases (~1.7-fold) in *Cntnap2* promoter function. All three variants localize to the binding site of the transcriptional repressor neuron restrictive silencer factor (NRSF) and its cofactor SYN3A. The authors propose that variation in the transcription factor binding site of NRSF and SYN3A act as a protective factor by altering expression of *Cntnap2*.

Andreas Chiocchetti (Goethe-University, Frankfurt, Germany) presented research related to the role of a rare *Rpl10* mutation in ASD. This group found two missense mutations in exon 7 of the ribosomal protein *Rpl10* in a mutational screen of families with ASD. Further, these mutations alter the translational capacity of the ribosome [Klauck et al., 2006; Chiocchetti et al., 2011]. These authors sought to find which pathways are affected by the specific mutations and if any overlap with other disorders. Using lymphoblasts, they screened for proteins with altered overall expression and change in abundance between individuals harboring the mutation versus controls. Alterations were found in protein isoforms relevant for glucogenesis, oxidative stress, and mRNA. It appears that *Rpl10* deficiency mimics oxidative stress.

Dr. Derek Morris (Trinity College, Dublin, Ireland) presented results of next-generation sequencing of the exonic regions of 215 putative susceptibility genes in 151 Irish cases of ASD, 273 of SCZ, and 287 controls. The authors sought to identify rare mutations contributing to one or both disorders, given the similar phenotype and underling genetics of the two disorders. They found that 29 of the cases carried LOF variants. A de novo nonsense variant was found in *Grin2B* as well as LoF variants in neurexin in nine cases. This research furthers the evidence for association of these genes with ASD and SCZ.

Other Childhood Psychiatric Disorders (Reported by Katri Kantojärvi)

Dr. Cynthia Bulik (University of North Carolina at Chapel Hill) presented GWAS results on anorexia nervosa (AN). AN is a debilitating and potentially lethal mental illness (prevalence ~1 in women; sex ratio ~9:1; heritability estimates 22–88). This collaboration between The Genetic Consortium for Anorexia Nervosa (GCAN) and Wellcome Trust Case Control consortium (WTCCC3) conducted the largest GWA in AN thus far. Genotyping was completed on 2,907 AN cases and 14,860 controls. Controls were carefully selected to match cases geographically. No SNPs reached genome-wide significance in the discovery analysis nor in a meta-analysis of the discovery and European replication datasets comprising a total of 4,883 cases and 20,653 controls. A sign test with an independent WTCCC3 anorexia replication sample (1,860 cases) revealed 80% of SNPS were in the same direction as the discovery meta-analysis (binomial *P*-value 0.000001). Additional collection of AN cases are planned.

Dr. Christel Middeldorp (Biological Psychology, Vrije Universiteit) discussed a genome wide meta-analysis of internalizing problems at age 3. Internalizing problems which are highly heritable were assessed with the internalizing problem subscale of the Child Behavior Check List (CBCL). GWAS data were available for 1,594 twins from the Netherlands Twin Register (NTR), 2,037 Dutch unrelated individuals from Generation R (GenR) and 1,084

individuals from Raine, Australia. Methods used in analyses were PLINK, METAL, VEGAS, and Ingenuity. No single SNP reached genome wide significance. The most promising results appeared on chromosome 9q33.1 in an intergenic region and on chromosome 20p12.1 at the *PCSK2* gene with several SNPs having a *P*-value below 1×10^{-4}. Genes associated with adult psychiatric symptoms appeared to be associated with internalizing problems at age 3.

Dr. Iiris Hovatta (University of Helsinki) presented her study which investigated if childhood adversities affect adult age leukocyte telomere length of the Finnish population. Several recent studies, but not all, have shown that childhood stress is associated with shorter leukocyte telomere length (LTL) later in life. However, it is unknown whether childhood stress and consequently shorter LTL are important on a population level. This study hypothesized that the number of childhood adverse life events predicts shorter LTL at adult age and investigated this hypothesis in an epidemiological health 2,000 cohort that represents the entire Finnish population. The subjects were collected during 2000 and 2001 to assess the major public health problems, functioning and their determinants of the adult Finns, aged 30 years or older. Childhood adversities were assessed with a questionnaire containing a series of 11 questions regarding the childhood social environment before age of 16. Relative LTL was determined from genomic DNA extracted from peripheral blood by a quantitative real-time PCR-based method. After quality control, the sample consisted of 5,799 individuals with information available on childhood adversities and LTL. Relatively common childhood adversities were associated with shorter LTL at adult age, and this effect can be detected in a nationally representative population-based cohort.

Dr. Anke Hinney (Department of Child and Adolescent Psychiatry, University of Duisburg-Essen) presented the results of the genome-wide analysis of rare copy number variations in ADHD (Attention Deficit Hyperactivity Disorder). ADHD represents one of the most common psychiatric disorders in children and adolescents with a worldwide prevalence rate of 5.2% [Polanczyk et al., 2007]. A genome-wide CNV association study included 489 patients with ADHD and 1,285 population-based controls. Methods used were based on Illumina SNP arrays (ADHD patients: Human660W-Quadv1, controls: HumanHap550v3). Replication of the findings was conducted in an independent sample of 386 ADHD patients and 781 healthy controls. In global burden analyses of rare CNVs stratified by their size, a trend for an association between large (>500 kb), rare (freq $\leq$ 1%) CNVs, and ADHD. The study revealed one genome-wide significant region within the *PARK2* gene at chromosome 6 with a *P*-value of 1.18×10^{-4}. Mutations and CNVs in *PARK2* are known to be associated with Parkinson disease.

Dr. Anita Thapar (Cardiff University) talked about a shared polygenic contribution between ADHD in childhood and SCZ. This group has previously shown overlap of structural genomic variation (CNVs) between SCZ and childhood attention deficit hyperactivity disorder (ADHD). The present study investigated possible source of genetic overlap, namely, common polymorphisms between ADHD, BD, and SCZ. The study consisted the recently published PGC GWAS analyses for SCZ and for BD as the discovery sets on which to define polygenic scores that were assigned to each individual in the UK ADHD GWAS data set (727 cases, 2,067 controls). SCZ risk alleles were able to discriminate ADHD case individuals from controls ($P = 1.04 \times 10^{-4}$, $R^2 = 0.45\%$). They observed borderline evidence for discrimination between ADHD and controls using BP risk alleles ($P = 0.0519$, $R^2 = 0.11\%$). Strongest discrimination of ADHD cases from controls was provided by alleles that were risk alleles for both SCZ and BD ($P = 9.98 \times 10^{-6}$, $R^2 = 0.59\%$). The findings suggest the genetic relationship of ADHD may be closer to SCZ than it is to BP and indicate the need for further studies of the genetic architecture of psychiatric disorders across traditional diagnostic boundaries.

Statistical Methods and Bioinformatics (Reported by Eilis Hannon)

Dr. Nadia Solovieff (Massachusetts General Hospital) discussed the complication of neutral variation in studies of rare variants. She proposed focusing the analysis on recent mutations and introduced a methodology for classifying singleton mutations found in a case control study as such. Data presented recovered 12% (of a maximum 20%) of validated de novo mutations from a trios study. When applied to a population-based study, stronger enrichments for synaptic and de novo gene mutations were found in the subset of LOF variants classified as recent for cases compared to controls.

Dr. Robert Power (King's College, London) explored the SCZ paradox using SCZ polygenic scores to predict reproductive fitness. A negative relationship was reported between the polygenic score and number of grandchildren, indicating that SCZ variants are under strong negative selection relative to other traits. In contrast, a quadratic rather than linear relationship was found with the depression polygenic scores.

Dr. Daniel Howrigan (University of Colorado at Boulder) investigated whether ROH contributed to SCZ etiology in the same way that common variants do. Having performed region by region analysis for ROH, the top 7 regions all predicted disease status. The combination of top ranked regions, akin to the polygenic score analyses, were better predictors than a whole-genome measure. However these results were biased by an individual's total ROH burden. After accounting for linkage disequilibrium, the results were not significant.

Dr. Wesley Thompson (University of California) presented the ideas and mathematics behind using a second GWAS to improve replication rates for genes with pleiotropic effect. He showed increased inflation in a SCZ GWAS, through QQ plots, for SNPs already showing some evidence of association with BP and vice versa. The relationship between these and the false discovery rate allows more SNPs to be detected at genome-wide significance, illustrated with the PGC datasets for SCZ and BP.

Dr. Danielle Posthuma (Vrije Universiteit) discussed how a gene's position in a molecular interaction network and its structural properties can be predictive of how strongly it influences disease, as seen in cancer genetics. Internet databases were mined for metrics characterizing genes associated to monogenic diseases, complex diseases, and those not currently associated with disease. Monogenic genes were the most central in interaction networks, with the highest connectivity, whereas non-disease genes were located on the periphery. Although complex disease genes had more exons and

isoforms this is probably due to a bias in GWAS as larger genes are more likely to be significant.

Dr. Larmie Duncan (Harvard School of Public Health) compared seven different annotation tools for variants from the Swedish Exome study. All passed a proof of principle test that more deleterious variants are less frequent in the population. In terms of variance explained, Mutation Tester performed the best, but the difference between methods was small. Using them in combination, for example by scaling all scores and adding, proved to be the best method. Continuous metrics performed better than categorical, and where multiple predictions were given, taking the worst was shown to be the best approach.

Cross Disorder Screening (Reported by Michael Way)

Results were presented of cross disorder and pathways analyses of the PGC genome wide association datasets for SCZ, BP, MD, AUT, and ADD of over 60,000 individuals with high quality raw genotype data.

Dr. Stephan Ripke (Massachusetts General Hospital; Broad Institute; Harvard University, USA) explained the rationale for cross disorder analysis following a previous polygenetic analysis, showing significant genetic overlap between all five PGC psychiatric disorders. Interestingly, the results showed less genetic overlap between the childhood (ADD, AUT) and adult (SCZ, BP, MDD) disorders. When the SCZ, BP, and MDD datasets were combined several loci met traditional significance levels ($P \leq 5 \times 10^8$). Predominantly, these loci have been reported previously and include calcium channel and micro RNA (miRNA) genes. The presenter finished by stating future plans such as replication of the combined SCZ, BP, and MDD meta-analysis findings within an independent data set with high quality raw genotypic data.

Dr. Phil Hyoun Lee (Massachusetts General Hospital, USA) gave findings from a network and pathway analysis of miRNA target gene associations within the combined PGC disorder datasets. The post-transcriptional regulatory functions of miRNA and their key roles in cognitive decline and neuronal differentiation were presented. This was highlighted by PGC findings in the SCZ cohort whereby nearly half of the strongly associated genes were post-transcriptionally regulated by *MIR-137*. One of the aims of this study was to identify miRNA targets enriched in the combined PGC dataset. Bioinformatic approaches were undertaken including a set-based enrichment test (INRICH), functional expression analysis, direct protein–protein interaction analysis, and GRAIL text-mining. Significantly enriched associations were observed for gene sets regulated by miR-9 and an overrepresentation of expression of these genes was found in the brain.

Dr. Gerome Breen presented findings from a combined pathway analysis of the PGC cross disorder dataset. Gene sets were accessed from a variety of sources including KEGG, GO, Reactome, PANTHER, OMIM, and Targetscan. The presenter mentions how only 60% of genes have a traditional pathway assigned. Different pathway analysis methods were used including ALLIGATOR, INRICH, MAGENTA. Associations were found for different pathways in each disease studied, however none met genome wide significance. Findings included circadian rhythm pathways for ADD, digestive processes with AUT, cell junction organization with MDD, histone H3-KL methylation with BP, and post-synaptic density pathways with SCZ. A combined pathway analysis of different disease datasets was also performed which proved to be more robust when the adult disorders (SCZ + BP + MDD) were combined. One hundred four pathways met genome-wide significance, with significant overlap between pathways implicating roughly a dozen independent processes, including the WNT signaling pathway. When both adult and childhood disorders were combined nearly 800 overlapping pathways were significantly associated with disease, including the Ras pathway and multiple processes involved in calcium signaling and the regulation of cell matrix adhesion.

Dr. S. Hong Lee (Queensland Brain Institute, AU) presented a novel approach for GWAS pathway analysis using genomic partitioning by functional annotation of variance and covariance. This approach includes all variants from a GWAS dataset, independent of their effect size. Using an updated version of GCTA software and the combined PGC data, this novel model was applied. Results found central nervous system (CNS) pathways and processes were represented, for example, brain expressed-, synapse-, and neuronal-gene sets. Normal probability theory was used to test for significance with the finding that CNS pathway genes were significantly associated with SCZ and BP in comparison with other genic and non-genic SNPs.

Dr. Naomi Wray (University of Queensland) discussed pleotrophy between single-nucleotide polymorphisms (SNPs) for five psychiatric disorders. She sought to answer the question of whether patients with psychiatric illnesses were more genetically related to each other than to controls. She compared 12 million pairs of genes using ''SNP-Chip'' technology to estimate heritability. To further add to the strength of the findings, a sanity check was done by comparisons with Crohn's disease which yielded a bivariability of almost zero. The highest bi-variability was seen in SCZ and BP. Fifteen percent of patients first diagnosed with BP ended up with a stable SCZ diagnosis. Five percent of schizophrenics ended up with a BIP diagnosis. Because of this diagnosis overlap, this correlation was expected. The other top bivariability was seen with BP and MDD. The study found a surprising negative relationship between autism spectrum disorder and attention-deficit-hyperactivity disorder, which they were unable to explain. The study was limited by a small sample size for the childhood diseases.

Epigenetics (Reported by Katarzyna Mantha)

Dr. Vanessa Nieratschker (Central Institute of Mental Health, Mannheim, Germany) reported on the influence of the epigenome on stress and its impact on developing depression. She discussed the POSEIDON (**P**re-, peri, and p**O**stnatal **S**tress in human and non-human offspring: a translational approach to study **E**pigenetic **I**mpact on **D**epressi**ON**) study, which compares methylation patterns in humans, rodents, and non-human primates [Nieratschker et al., 2012]. Dr. Nieratschker presented the results of methylated DNA immunoprecipitation (MeDIP) analysis with a custom promoter tiling array and found 3,400 differentially methylation genes between highly stressed and non-stressed subjects. Twenty-three genes overlapped between human samples and Rhesus monkeys. One gene, *MORC1*, was found to be demethylated in all three

species. Dr. Nieratschker emphasized new candidates for stress-associated disorders can be found by using these technologies [Rietschel et al., 2010].

Dr. Janice Fullerton (Neuroscience Research Australia, Sydney, New South Wales, Australia) presented her study on the identification of genetic and epigenetic risk factors for BP. She selected 39 genes (49 SNPs) from the PGC-GWAS [Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011]; for allele comparison between at-risk and control individuals using PLINK [Purcell et al., 2007]. Using a methylation array for at-risk and control individuals, Dr. Fullerton found no significant differences in methylation status. Of interest, she observed two individuals in her Risk Burden Analysis who she described as being in the ''transition state'' towards BP. When asked if she might further examine methylation differences in these two individuals, she stated that this would give her low power, and it would be more productive to wait until sample size increased.

Dr. Melanie Carless (Texas Biomedical Research Institute, San Antonio, USA) introduced her study discerning the role of DNA methylation in memory and learning. She included premorbid and first degree relatives in the assessment of methylation profiles [Carless et al., 2011]. Her collaboration with Dr. David Glahn (Yale University School of Medicine, New Haven, USA) and Dr. John Blangero (Texas Biomedical Research Institute, San Antonio, USA) has led to a pilot project using 187 individuals and the assessment of 1,505 CpG sites in 807 genes. Dr. Carless identified 22 associations with declarative memory, including methylation within *ALOX12* (memory-related) and *BDNF* (depression-related). An overabundance of well-known Alzheimer disease genes was also identified, including *APP* and *APOA1* (spatial working memory).

Dr. Murray Cairns (The University of Newcastle Australia) noted that SCZ is a complex neuropsychiatric disorder involving disturbances in neural circuitry and synaptic function. While there are likely to be many genes and developmental pathways leading to the neurobehavioral syndrome, the redundancy of these networks means that many combinations of gene variants have the potential to play a role. Recent investigation has revealed that post-transcriptional gene regulation and associated small non-coding microRNA (miRNA) are likely to be important factors shaping the topography of these networks. miRNA display complex temporospatial expression patterns in the mammalian brain and have the potential to regulate thousands of target genes by functioning as the specificity factor for intracellular gene-silencing machinery. Their dysregulation could also lead to pervasive changes in the network structure during development and in the mature brain that are significant in the pathophysiology of SCZ. This is now supported by compelling evidence that the underlying miRNA biogenesis machinery and miRNA genes themselves, are subject to disease-associated genetic mutation and epigenetic influence. He examined the neurodevelopmental trajectory of miR-137 expression in the normal human and rat prefrontal cortex, and the affect of this variant on cognition and cortical expression of the mature miRNA. These analyses reveal a complex dynamic developmental expression pattern and significant mutation associated changes in cortical expression and cognitive phenotypes in SCZ. These findings are supportive of a role for miRNA in SCZ and suggest that they may have significance as biomarkers or as targets for pharmacological manipulation.

Dr. Roel Ophoff (UC, Los Angeles) performed a study using whole blood to gain a better understanding of causal relationships between genetic variation and DNA methylation profiles. To examine the association between DNA methylation and genetic variants, genomewide genotype and DNA methylation (27K Illumina array) data was obtained from whole blood of 260 SCZ patients and 240 healthy controls. For a subset of these subjects array-based gene expression data was available as well. By combining epigenetic and gene expression data they identified almost 700 CpG sites in the genome that are differentially methylated between SCZ patients and unaffected controls, and of which methylation status is associated with gene expression levels; moreover, these genes are also differentially expressed between cases and controls. Genetic analysis revealed that some 8% of these CpGs are under local (*cis*) genetic control. They hypothesized that identification of biological relevant links between DNA methylation and gene expression in the context of disease might serve as an efficient way to enrich for disease susceptibility loci if under genetic control (methylation QTLs, mQTLs). They used the available results of the large PGC SCZ genome-wide association (GWAS) study to examine whether the observed mQTLs represent disease association signal. They observed significant enrichment of SCZ association signals of mQTLs with the most significant effects for those loci that are also associated with differential gene expression in cases and controls. While the enrichment effects were already visible when using nominal significant thresholds ($P < 0.05$ in PGC) the effects were amplified at more stringent values (e.g., $P < 1E{-}4$). They identified five disease-associated loci that control DNA methylation in *cis*, which in turn affect gene expression in a case/control study. Interestingly.One of these loci was previously identified to be involved in disease susceptibility in the recent PGC SCZ GWA study. Our results suggest that enrichment of biological signal by combining genetic, epigenetic, and gene expression profiles from whole blood may be an efficient approach to identify disease susceptibility loci including neuropsychiatric traits.

Dr. Torsten Klengel (Max-Planck Institute of Psychiatry) delineated an epigenetic mechanism for a gene x environment (GxE) interaction of the FK506 binding protein 5 (*FKBP5*) gene with childhood abuse on the development of PTSD in adulthood. Data from this study were collected as part of the Grady Trauma Project and replication was performed by the Conte Center Study for the Psychobiology of Early-Life Trauma (Emory University, Atlanta, GA, USA). He showed that *FKBP5* polymorphisms interact with child abuse exposure for the development of current PTSD symptoms in adulthood. The risk to suffer from lifetime PTSD is significantly increased by exposure to early trauma in *FKBP5* risk allele carriers, but not in carriers of the protective genotype. Pyrosequencing of bisulfite treated DNA of highly traumatized individuals and controls revealed a significant demethylation of CpGs around glucocorticoid responsive elements (GREs) of *FKBP5* in abused individuals. Further, they found a significant interaction of *FKBP5* genotype and childhood abuse on DNA methylation levels in 3 CpGs in intron 7 ($F(74,1) = 37.8$, $P_{corr} < 0.001$). Replication in an independent cohort from the Conte Center Study confirmed these findings. In a multipotent human hippocampal

progenitor cell line they demonstrated that *FKBP5* demethylation is initiated by GR-activation with dexamethasone which leads to a highly significant DNA demethylation in CpGs in intron 7 similar to the CpGs affected by early trauma in *FKBP5* risk allele carriers (average of 17.1% demethylation in the 3 CpGs, $P < 0.001$). They extended these results comparing DNA methylation changes in dexamethasone treated hippocampal progenitor cells with trauma exposed individuals on Illumina's 450 k methylation chip. In summary, *FKBP5* increases the risk of developing PTSD by allele-specific, childhood trauma-dependent demethylation of CpGs in functional GREs of *FKBP5*. It is interesting that the effects on DNA methylation seemed to be restricted to exposure to childhood trauma and were not influenced by traumatic experiences in adulthood, suggesting a possible sensitive period in early development for these epigenetic effects.

Phenotypes/Endophenotypes (Reported by Suzanne Gonzalez, Eszter Kótyuk, and Cybele C.P. Wong)

Cognitive/clinical endophenotypes. Professor Trevor Robbins (University of Cambridge) spoke on neurocognitive phenotypes. These can be linked to unique neural circuitry that may become dysfunctional in a disorder. Candiate gene studies try to identify association of there characteristics with one or more genetic variants (risk genotypes). Well established endophenotypes refine diagnostic classification and increase the power to identify specific causative genetic variants. As an example, impulsivity contains impulsive choice, steeper reward discounting, delay aversion, lack of consideration when making decisions, change in response criterion, and timing impairment. Impulsivity is linked to the mesolimbic dopamine reward system [Buckholtz et al., 2010] and the ventral striatum [Dalley et al., 2007]. An animal model [Dalley et al., 2007] suggests that a form of impulsivity in rats predicts high rates of cocaine self-administration and is associated with changes in dopamine function before drug exposure. Their data demonstrated that trait impulsivity predicts cocaine reinforcement and that D2 receptor dysfunction in abstinent cocaine addicts may be partly determined by premorbid influences. According to these results on a clinical level high impulsivity could be a good endophenotype for human stimulant abuse [Ersche et al., 2010; Dalley et al., 2011].

Impulsive control can be measured with Logan's stop-signal reaction time task [Aron et al., 2003]. When defining neural networks associated with "stopping" impulsivity, the neural circuitry that contributes to impulsivity could be an obvious objective in the search for neurocognitive endophenotypes of drug addictions [Dalley et al., 2011]. There is evidence that "stopping" impulsivity is a good endophenotype for stimulant drug addiction maybe because impulsivity has the same underlying neurocognitive circuity as stimulant addiction: Ersche et al. [2012] found abnormalities in the fronto-striatal brain systems in both stimulant-dependent individuals and their siblings without any history of chronic drug abuse implicating that this neurocognitive region is of vital importance in self control. Other work has identified seven networks underlying impulse control and found that different networks were associated with different aspects of impulse control [Whelan et al., 2012]. Their findings suggest that impulsivity is a multi-dimensional construct, and it is plausible that distinct brain networks contribute to different cognitive, clinical, and behavioral aspects of impulsivity.

He also discussed compulsivity an endophenotype linked to obsessive-compulsive disorder (OCD), SCZ, and autism. Compulsivity contains stereotypy, rigid strategies or attentional set, inappropriate persistence of habits (despite outcome devaluation or negative consequences) and perseveration in reversal learning [Dalley et al., 2011]. Compulsivity as an endophenotype can be measured with cognitive flexibility tasks for example the CANTAB ID-ED or the Wisconsin card-sorting test. It is clear from animal studies that the prefrontal cortex has multiple functions in inhibitory control, a cognitive function closely related to compulsivity. In monkeys lesions in different regions of the prefrontal cortex caused loss of inhibitory control in different behaviors: attentional selection or affective processing [Dias et al., 1996]. Also, there is evidence from human fMRI studies that extra dimensional set shifting and reversal learning involve different prefrontal cortex circuity [Hampshire and Owen, 2006]. Studies have shown that OCD patients have reduced bold response in the orbitofrontal cortex during reversal learning. It appears that compulsivity is a good endophenotype for OCD [Chamberlain et al., 2006] but not for SCZ [Ceaser et al., 2008]. But there is cognitive impairment in SCZ as well which can be measured with CANTAB self-ordered Working Memory task [Pantelis et al., 1997]. The CANTAB paired associates learning task is also a good endophenotype to measure and distinguish hippocampal deficits in AZ, depression and dementia [Swainson et al., 2001]. Thus, Professor Robbins was emphasizing that using a cross-dimensional endophenotype approach instead of DSM defined categories make it possible to refine diagnostic classification. Research should focus on dimensions and symptom clusters rather than DSM categories. Researchers should employ several independent measures of the examined theoretical construct. Research should be built on some prior familial basis for the construct, it should combine objective behavioral, cognitive and neural measures to get a good phenotype.

Dr. Ole Andreassen (University of Oslo and Oslo University Hospital-Ulleval, Oslo, Norway) reported findings that TCF4 sequence variants and mRNA levels are associated with neurodevelopmental characteristics in psychotic disorders [Wirgenes et al., 2012]. TCF4 mRNA expression level in peripheral blood was compared between a large sample of patients with psychosis spectrum disorders and healthy controls. TCF4 risk variants were tested for association using a linear regression model with characteristic psychosis phenotypes (neurocognitive traits, psychotic symptoms and structural MRI brain morphometric measures). TCF4 mRNA expression level was significantly upregulated in all psychotic diagnostic groups compared to controls. The rs12966547 and rs4309482 risk variants were associated with poorer verbal fluency in the total sample. There were significant associations of 14 other exploratory TCF4 SNPs with negative symptoms, cognitive dysfunction and cerebellar volume in the SCZ sample, AAO in total patient sample and variants correlating with temporal cortical area and brain volume in total sample. These results implicate TCF4 in psychosis, presumably related to abnormal neurodevelopment.

Dr. Emma Knowles from the Yale University modelled cognition in a Mexican American population (N = 1,269, 63% female). She identified four quantitative trait loci (QTLs), of which two QTLs (8q24.22 and 8q21.11) for working memory and general intellectual ability on chromosome 8 reached genome-wide significance. Another two QTLs (17q23.2 and 17q24.1) identified on chromosome 17 were associated with spatial and general memory performance. According to Dr. Knowles, a gene called HEY1 located at 8q21 is associated with memory and β-amyloid metabolism. It might provide us some idea on the functions of the identified QTLs.

Brain imaging endophenotypes. Dr. Sven Cichon (University of Bonn and Research Center Juelich, Germany) reported on the systematic search for genetic factors influencing the thickness of the cerebral cortex, in which the research group sought to identify gene variants contributing to inter-subject variability in order to elucidate the molecular mechanisms underlying brain functions. Genotypes were correlated with the phenotypic variability that was assessed through MRI in a total of 158 healthy volunteers. They focused on cortical thickness (CT) which is a heritable, quantitative trait, assumed to reflect the architecture of neuronal and glial cells in the cortex [Winkler et al., 2010]. They applied a principal component analysis (PCA) on the pooled data from both hemispheres of 126 cortical regions. They performed a GWAS focused on 1st principal component, as it explains 60.7% of the observed CT variance. A total of 14 SNPs were identified in this discovery phase and mapped to their respective region of interest (ROI). A total of 10 ROIs were identified. The top two SNPs located in 10q25 between SORSC1 and XPNPEP1 mapped to the primary motor cortex of the posterior portion of the frontal lobe. The top SNP showed association close to the formal threshold for genome-wide significance ($P = 6.98E{-}8$) and was significant after correction for multiple testing using Monte Carlo simulations ($P = 0.04$). Other genes highlighted in this study are JARID2 (near DTNBP1) and ZNF804A, which have previously been implicated in SCZ [Pedrosa et al., 2007; O'Donovan et al., 2008].

Dr. Sarah Medland (Queensland Institute of Medical Research, Brisbane, Australia) presented results from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium, a network established in 2010 to bring together researchers in imaging genomics to increase the understanding of brain structure and function. Imaging and genetics protocols were developed to ensure data harmonization between working groups (http://enigma.loni.ucla.edu/protocols/). The ENIGMA 1 Consortium performed genome-wide association meta-analyses and replication for mean bilateral hippocampal, total brain, and intracranial volumes [Stein et al., 2012]. Meta-analysis with ENIGMA discovery and replication samples from the CHARGE Consortium resulted in an intergenic variant rs7294919 (12q24.22) that was associated with hippocampal volume and rs10784502 within the HMGA2 gene was associated with intracranial volume. The working group developed a freely available online interactive tool, EnigmaVis, in order to visualize the association results alongside allele frequency, genes, and functional annotations [Novak et al., 2012]. They are currently under way with ENIGMA 2 which consists of 28 different sites and over 13,000 individuals and focuses on seven subcortical regions and intracranial volumes with a genetic focus on the 1000 genomes project (phase1 version 3) [1000 Genomes Project Consortium, 2010].

Dr. Stephanie Le Hellard (Centre for Advanced Study, Oslo, Norway) discussed contributions from the Norwegian Cognitive Neuro Genetics sample (NCNG) [Espeseth et al., 2012] in the polygenic deconstruction of psychiatric disorders with neurocognitive gene sets. A GWAS was performed on a sample of 700 healthy individuals of Norwegian origin which had been extensively phenotype for neurocognitive abilities and brain imaging, followed by replication in an additional 4,000 samples. Several studies were performed to identify genes implicated in general cognition, in reaction time, speed of processing, memory, and in brain imaging. They selected gene sets associated to several cognitive domains (general cognition, verbal abilities, speed of processing, reaction time, memory), and identified and replicated significant enrichment across SCZ or BP samples for specific neurocognitive associated gene sets.

Dr. Vidar M. Steen (University of Bergen, Norway) led a discussion on the future of genetics of imaging and neurocognitive phenotypes. The overall consensus is that endophenotypes are very complex traits. The main driving force for power is sample size; therefore, studies should have adequate samples and large collaborations are encouraged. Stringent quality control measures and standardized protocols are needed.

Dr. Philip Mitchell (University of New South Wales) presented the latest findings of the BP Kids & Sibs longitudinal study in Australia. Subjects who were "at risk" for BPs (with at least one first-degree relative with BP, N = 48) and healthy controls (N = 49) performed a facial-emotion Go/No-Go fMRI task. The "at risk" subjects showed reduced activation at inferior frontal gyrus (IFG) when inhibiting responses to fearful faces ($P = 0.009$, FWE-corrected). Association analyses revealed SNP rs10776799 in nerve growth factor (NGF) was associated with the IFG activation ($P = 0.071$). SNP rs2283265 in dopamine D2 receptor (DRD2) was associated with larger total cortex volume ($P = 0.015$) and risk allele carriers of rs1006737 in CACNA1C showed increased grey mater density in right amygdala and hypothalamus. These studies demonstrated the genetic basis of cognitive deficits in siblings of patients with BP.

Dr. Eva Janousova (University of Bergen, Norway) and colleagues applied sparse reduced-rank regression (sRRR) model, a recently developed multivariate approach, to identify genetic markers for SCZ in the Norwegian Cognitive NeuroGenetics sample (N = 440, 34.8% male). The sRRR model allowed simultaneous modelling of all genetic markers with scores for the Digit Symbol Substitution (DSS) test, brain cortical thickness, and surface area. The sRRR model identified a set of 29 SNPs that were associated with the neuroimaging traits, of which 14 of them assigned to genes as defined by Ensembl Version 54. One of the top-hit rs3911890 was mapped to SOX13 gene, suggesting its potential role in neurodevelopment.

Dr. Falk Kiefer (Central Institute of Mental Health, Mannheim) illustrated the association between SNP rs1327367 and responsiveness to alcohol cues in amygdala in alcohol-dependent patients (N = 81, 57 males). SNP rs1327367 is located in a gene that encodes transcriptional factor GATA4 in atrial natriuretic peptide (ANP). The risk allele carriers (AG/GG, N = 46) showed significantly lower

alcohol cue-induced activations in amygdala. As revealed by a survival analysis, the AA carriers are less likely to experience relapse in alcohol drinking ($P = 0.018$). This study demonstrated the role of GATA4 in alcohol addiction.

Neurochemical factors. Dr. Jurjen Luykx from the University Medical Centre Utrecht and colleagues conducted the first GWAS to identify genetic variants influencing the levels of NDMAR co-agonists—glycine, L&D-enantiomers of serine, proline, and alanine in plasma and cerebrospinal fluid (CSF) on 414 healthy subjects. Four genome-wide significant loci were detected around genes encoding for transporters and enzymes including PRODH, SLC6A20, and DAO. In addition, hypothesis-driven QTL analysis revealed the association between rs7598440 in ERBB4 with the CSF GABA level in the subset of sample (N = 151) [Luykx et al., 2012]. Despite the lack of replication sample as pointed out by Dr. Luykx, the results have supported CSF as an informative target to study GABA activity in human.

Next Generation Sequencing (NGS) Studies (Reported by Iordanis Karagiannidis, Biju Viswanath, and Michael Way)

Dr. David Porteous (University of Edinburgh) presented his NGS work on the DISC1 locus in mood and psychotic disorders. Multiple previous studies [Chubb et al., 2008; Bradshaw and Porteous, 2011] have found this locus to be a genetic risk factor for many psychiatric illnesses (e.g., SCZ, BP, major depression) and quantitative traits (e.g., p300, grey matter density, hippocampus volume). He presented his findings following a comprehensive analysis of DISC1 structure–function and genotype–phenotype correlations from resequencing 528 kb of the DISC locus in over 1,542 subjects (240 with SCZ, 221 with BP and 192 with recurrent major depression, plus 889 healthy controls who are part of the Lothian Birth Cohort of 1936 (IQ measures at age 11 and repeat IQ, plus extensive additional measures of behavior and cognition at ~70 years of age). All individuals were sequenced to >80% coverage and >30-fold read depth. This analysis identified 708 common and 2010 rare DISC 1 locus variants. Association analysis revealed significant association of rs16856199 with recurrent major depression, but no evidence of locus wide association with SCZ/BP. This finding could not be replicated in a community-based sample.

Dr. Richard McCombie (Cold Spring Harbor Laboratory) highlighted the importance of family genetics as a unique resource to minimize the time to find genes causing diseases. Although case–control studies are very valuable, large sample sizes are required due to the genetic heterogeneity contributing to psychiatric disorders. He explored several family-based strategies, using both trios and extended families to identify candidate genes. He described the exome sequencing of 57 SCZ trios, which identified significant enrichment of denovo mutations in genes having important roles in epigenetic regulation and chromatin modification (e.g., MECP2, CHD8, MLL2, TDRD5). The significant overlap between recent exome studies of SCZ [Hosak et al., 2012] and autism [Connolly et al., 2012] was also noted. The combination of family studies followed by targeted sequencing in case–control cohorts represents a powerful approach to understanding the genetics of psychiatric disorders.

Dr. Fernando Goes (Johns Hopkins University School of Medicine) reported progress of a large ongoing exome sequencing study of familial BP, using complementary family-based and case–control methods. While GWAS studies identified possible common variants of modest effect, ''bulls eye'' exome sequencing identifies low frequency/rare variants with intermediate effect. Analysis of data from 322 cases and 435 controls was presented. Bioinformatic annotation was performed using three programs: SIFT, VEST, and Polyphen. Top findings (e.g., ARID4B, STX10, RFPL4B, ATP5A1, APP) were not genes implicated in BP. Recent GWAS findings [Goes et al., 2012] were also not replicated. Pathway analysis to test for enrichment of rare functional variants in gene ontology categories did not reveal any significant findings. However, these findings are only an interim analysis. It is hoped that increasing the sample size, ongoing family approaches, alternate analysis approaches, and focus on LOF variants will identify more replicable findings.

Dr. Pamela Sklar (Mount Sinai School of Medicine) presented data from a large scale whole exome sequencing study of BP in 1,110 Swedish patients and 2,438 matched controls from an ongoing SCZ sequencing study. Genome-wide association studies (GWAS) focusing on common single-nucleotide polymorphisms have pointed to a polygenic basis for BP [Sklar et al., 2008]. This study focused on the role of rare coding variation (single point mutations, indels and structural variation), as assayed by high-depth next-generation sequencing. Preliminary analysis has not revealed any single alleles of large effect, but has identified a small set of nominally significant genes. An attempt to replicate the top 25 signals in the PGC [Sullivan, 2010] also did not reveal any significant findings.

Dr. John Kelsoe (University of California, Department of Psychiatry, San Diego, USA) presented findings from whole genome sequencing in an unusual BP family. The family had an interesting inheritance pattern whereby the rare autosomal dominant disorder medullary cystic kidney disease (MCKD) co-segregated with BP. Whole genome sequencing (30× coverage) was performed in probands (affected individuals) with the focus on causative mutations which mapped to linkage regions identified in this family. Several mutations of interest were identified however a mutation within *NTRK1*, a receptor tyrosine kinase involved with neurotrophic signaling stood out. Neurotrophic signaling processes have been associated with BP and lithium response previously and the mutation likely prevents SHC binding to a tyrosine on a phosphorylation domain crucial to protein function. This finding led to a second stage deep re-sequencing effort (HiSeq2000, 1000X read depth) of the *NTRK1* gene and the functionally related *NGF* gene in a case control sample. This yielded an increased burden of rare non-synonymous SNPs in *NTRK1* and *NGF*, however for more common SNPs there was no mutational burden.

Dr. James Potash (Carver College of Medicine, University of Iowa, USA) presented findings from whole exome sequencing of families and case control samples from what is now the bipolar genome Study (BiGS). Exome and synaptome promoter sequencing was performed in eight large families with 80% coverage at a 20× read depth. The primary goal of this study was to identify

"low hanging fruit," that is, rare variants which are predicted to be damaging and segregate within families. Numerous loci (*C3AR1*, *TADA1*, *AAPL1*) with high-risk mutations were identified, however nominal association signals were obtained giving little statistical power to the findings. An analysis of familial segregation of these as well as loci identified from GWAS (*CACNA1C*, *ANK3*) was also performed. Some markers marginally segregated, and these results did not survive multiple correction. The best candidate genes from this study are *ABHD12B*, *CDK1S*, *DCHS1* however he concluded that there were no "low hanging fruit" in these data.

Dr. Margit Burmeister presented a summary of the research aims and on-going findings from the Bipolar Research in Deep Genome and Epigenome Sequencing (BRIDGES) study. One of the primary goals of this study was to develop novel approaches for analysing whole genome sequencing datasets. Sequencing was performed with 8–10× coverage in 1,600 European Bipolar type 1 cases and 1,600 screened controls. High levels of quality control were undertaken in this study to avoid sources of experimental error including DNA extraction from blood, using principle component analysis and the use of bar coded plates. The primary result was that there was no excess of rare variants where common associations have previously been reported through GWAS. Secondary to this a SKAT[5] gene based test was also performed with no significant findings.

Dr. Seth Ament (Institute for Systems Biology, USA) presented findings from the family genome sequencing project. The primary hypothesis underlying this study was that sequencing within multiplex families provides an efficient route to family-specific genetic causes of BP. Whole genome sequencing was performed (60× coverage) on 142 individuals from 23 multiplex pedigrees. KAVIAR[6] and Ingenuity variant analysis were used to analyse novel variants that co-segregate with diseases in each family. Missense mutations were identified within *CHRNA3*, *ARVCF*, *NEGR1*. An extremely rare SNP (MAF < 0.001) was identified in *CACNA1C* resulting in a non-synonymous mutation (R1973Q). An analysis of most frequently mutated genes in eight families with BP also provided strong support for *CACNA1C*. A gene ontology analysis identified cell adhesion and nerve impulse processes overrepresented in the dataset. Another analysis was performed to test the monogenic nature of BP. This led to combined genome sequencing and linkage analysis in search for segregating variants in familial samples. However, no promising hits were identified. In summary, a variety of methodologies were presented for identifying causative mutations in familial samples.

Dr. M.O.' Donovan (Cardiff University) presented an approach to de novo mutations in SCZ using whole exome sequencing of 586 trios from Bulgaria. In order to partition the genomic variance attributable to SNPs in pathways he used the updated Genome wide Complex Trait Analysis tool. No substantial differences for rates of all classes of de novos across studies were observed. Weak enrichment for de novos compatible with a highly heritable disorder was observed. These data supported the specific synaptic pathways that were previously reported from de novo CNV analyses.

Dr. Guy Rouleau (University of Montreal) presented an approach for revealing the contribution of de novo mutations in developing specific neurodevelopmental disorders such as SCZ, autism spectrum disorders (ASD) and Intellectual deficiency (ID). He focused on the role of synaptic genes in the pathogenesis of the disorders ("Synapse-to-Disease" project). He found 28 singletons haing spontaneous mutations, some of which may be disease causing. On phase 2 of the project, four nonsense mutations were identified with exome sequencing at 14 trios from France. Both studies showed that de novo mutations can explain part of the missing heritability. More work is required for defining the pathways and the specific genes that predispose to these diseases and also that there must be significant genetic overlap between SCZ, AUT, and ID.

Dr. Aarno Palotie (Wellcome Trust Sanger Institute) presented a sequence analysis of SCZ and ASD in the UK10K Project. For SCZ a total of 1,700 cases have been gathered and also 430 familial cases form Finland including 150 samples from the Kuusamo isolate. For ASD over 800 cases have been selected. Then some results from a smaller sub-study of 77 autism trios (using the De Novo Gear Program) were shown. The de novo rates seemed to be consistent with other projects. A LOF variant was recognized in the CACNA2D3 gene. In the SCZ Finnish families, they found 8 of 22 families had a novel LOF variant co-segregating with the disorder and also four individuals had a homozygous deletion on 22q11.22.

Dr. Shaun Purcell (Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, United States of America) spoke about a whole exome sequencing approach in 5,023 cases and matched controls from a Swedish cohort. More deleterious alleles tend to have lower sample frequency. Analyses of genesets revealed the occurrence of true associations that may hide in the genome-wide distribution. Intersection of the data with protein-domain annotations and also the use of the identity by descent approach, combined with sequencing data can be used to detect de novo mutations. There is clear evidence for convergent genetic signatures in SCZ across CNV, GWA, de novo and population level exome sequencing studies and it will be necessary to combine these signals.

Substance Abuse and Environmental Stress (Reported by Eric Diehl)

Dr. James Dee Higley (Department of Psychology, Brigham Young University) focused on an insertion/deletion polymorphism in the promoter of the serotonin transporter gene *5-HTT* which moderates the effect of early life stress on depression. In humans, individuals who carry the short allele (the deletion) exhibit more depressive symptoms in response to early life stress than those who are homozygous for the short allele [Caspi et al., 2003]. Furthermore, this polymorphism is conserved in the rhesus macaque (*Macaca mulatta*) where it also interacts with early life stress [Bennett et al., 2002]. Dr. Higley began by explaining the importance of mothers in primate development. Maternal care is the primary interaction in the social world. Mothers provide the input at the necessary time for normal cognitive development; each material input coincides with brain development at that time. Without mothers (i.e., if macaques are peer-raised), infants are clingy, anxious, and impulsive. Further, the levels of CSF 5-H1AA (a serotonin metabolite) are increased in long/long individuals versus long/short who were peer-reared, and also over both genotypes who were mother-reared. Also, depressive and anxiety

phenotypes increase over 4 weeks in long/short, but not long/long infants.

The interaction of the polymorphism (termed *5-HTTLPR*) with early life stress is well replicated in primates, but humans have proved difficult to show an association. A meta-analysis found no interaction between *5-HTTLPR* and early life stress [Risch et al., 2009]. However two subsequent meta-analyses did find an interaction, but the effect size was quite small. This may be because of the heterogeneity of human environments. In non-human primates, the environment is much more controlled.

A primate model is ideal to study gene by environment interactions with alcohol. Long-term alcohol abuse has a heritability of between 50% and 60% [Ystrom et al., 2011]. Dr. Higley's model of non-human primate alcohol abuse uses a sweetened alcohol solution and vehicle available to the macaques for 5 days a week for 1 hr per day in the home cage. Ten percent to 20% of the subjects drink to intoxication, whereas 5–10% are averse to drinking. At first glance, it seemed that there was no effect of *5-HTTLPR* genotype on in the ethanol intake of peer-rear versus mother-reared macaques. However, when the rate of alcohol intake over 6 weeks was measured, the peer-reared long/short individuals showed a significant increase in intake over the other three groups at week six. Dr. Higley also showed a single-cage effect: the individuals caged alone drink more alcohol when peer-reared.

Aggression was measured using the monkey intruder paradigm. A macaque unknown to a group is placed in a cage next to the group cage of interest and aggressive behaviors are measured. All test subjects are the same sex. In males, aggression is directed toward the intruder, whereas in females it is directed to cage mates. In general, males are more aggressive than females, however; long/short males are more aggressive than any other group. Furthermore, aggression is escalated in the test animal if the intruder has the short allele. Females that have the short allele are aggressive to others in their cage.

Corticotrophin-releasing factor (CRF/CRH) is the primary initiator of the HPA axis, and causes anxiety when injected. Peer-reared monkeys show more CRF which increases across weeks of separation. A SNP in the *Crf* gene was shown to correlate with increased ethanol intake. Also, the high-activity MAOA genotype showed more ethanol consumption.

In conclusion, Dr. Higley's emphasized several major themes: Genes may be expressed differentially depending on the environment. Primate studies are very useful in that they account for double the variance (7–15%) when considering gene by environment interactions. Particularly, the homogeneous rearing and situational settings may in part account for some of the additional variance and explain some of the human studies failure to replicate. Interestingly, genotype of the initiator and the recipient must be considered in social interaction. Similarly, sex must be considered, especially when genotype is involved. Finally, the type of stressor is of importance when considering genotypic effects on behavior.

Animal Models (Reported by Laramie Duncan and Benjamin I. Laufer)

Dr. Kerstin Lindblad-Toh (Science for Life Laboratory Uppsala and the Broad Institute of MIT and Harvard) described findings from research about genetic influences on behavioral phenotypes in dogs. She explained that dogs are a useful model organism for behavioral phenotypes because of the way in which their phenotypes were shaped. Specifically, modern dog breeds exist as a result of selective breeding for desired traits such as herding, wrinkled skin, and retrieving, among many others. Selective breeding imposes severe selection and results in genes of relatively larger effects on phenotypes than those seen in humans.

An important consequence of the larger effect sizes (for loci affecting behavioral phenotypes selected in dogs) is that substantially smaller sample sizes are needed to identify genome-wide significant loci. For example, hundreds of samples can be used instead of tens of thousands of samples. Specific results were reported for dog domestication genes in a sample of 12 wolves and 60 dogs (from five different breeds). In this sample they identified 39 regions with 129 genes that met criteria for genome-wide significance. When these genes were further analyzed to determine which functional categories were overrepresented, two pathways emerged: (1) nervous system development, and (2) digestion. These pathways are interesting because they make sense in light of dog domestication.

In particular, Dr. Lindblad-Toh's group hypothesized that advantageous mutations in genes involved in the digestion of starch would have been selected for given their effect on dogs' ability to benefit from consuming humans' food. Consistent with this idea, they found evidence implicating mutations in genes in three key components of the starch digestion pathway: MGAM (maltase digestion), AMY (amylase), and SGLT1 (sodium glucose co-transporter (1). Her approach involved identification of increased F_{ST} and decreased heterozygosity, which are both signatures of selective sweeps.

Dr. Clarissa Parker (University of Chicago) presented her groups research on advanced intercross lines in rodent models (AIL) that give the advantage of splitting up genetic linkage and allowing for a higher mapping resolution [Parker et al., 2011]. In this research they use their model to examine the acquisition of learned fear, which is heritable and more difficult to extinguish in humans with PTSD [Zovkic and Sweatt, 2012]. They used two genetically distinct AIL populations to fine-map QTLs associated with fear conditioning. Using this model they examined whether any QTLs were associated with tone shock conditioning using the package r/QTLRel [Cheng et al., 2011]. By exploiting the increased recombination frequency of their AIL, they replicated and mapped QTLs with greater precision than previous approaches and identified multiple candidate genes. Ultimately, their approach can be generalized to many high throughput phenotypes. They hypothesize that the use of outbred strains in combination with GWAS could vastly accelerate the process of gene identification, as it causes a breakdown of linkage disequilibrium.

Currently, there is an incomplete catalogue of mouse CNVs and the objective of Jin Szatkiewicz's (University of North Carolina at Chapel Hill, USA) groups' research is to generate a comprehensive (162 strain, high resolution) and accurate (large scale validation) mouse CNV catalog. In their catalogue they sought to have 100 classical strains and 62 wild derived strains. This allows them to see both rare and common variants and use a population-based approach to discover CNVs. They conducted a genome-wide survey of CNVs using the Affymetrix Mouse Diversity Genotyping Array

[Yang et al., 2009]. They developed an analysis protocol that combined microarray data with computational algorithms and genomic resources to predict CNVs. In total, 1,499 copy number variant regions (CNVRs), spanning 1.5% of the mouse genome, were observed. This use of this catalogue for psychiatric genetics was exemplified by the groups establishment of the copy numbers across the 162 strains for Glyoxalase 1 (*Glo1*), as a duplication of *Glo1* has been implicated in anxiety-like behavior in mice [Williams et al., 2009]. The Sanger data (http://www.sanger.ac.uk/resources/mouse/genomes/) contains the sequence for 17 inbred strains and data on the CNVs present and has the potential to be used for validation of the groups results.

Recent research has found a genome-wide association between the Neurocan (NCAN) gene and BP [Muhleisen et al., 2012]. NCAN is one of few genes observed to be associated with both BP and SCZ. Given that there is the same risk variant for two different disorders, these preliminary findings hint that NCAN has integral brain functions. The aim of Dr. Sandra Meier's (University of Bonn, Germany) groups' study was to characterize NCAN by exploring the behavioral phenotype of *Ncan* knock-out (*Nca*n−/−) mice. They found that the NCAN risk allele is associated with the mania factor dimension, in particular with the sub-dimension of over-activity. *Ncan*−/− mice showed behavioral abnormalities strikingly similar to human mania endophenotypes, which were found to be reversible by lithium treatment.

ZNF804A has been identified as a candidate gene for SCZ and BP in replicated GWAS studies [Steinberg et al., 2011] and through patient specific searches for CNVs. It has a DNA binding domain, which suggests that it can act as a transcription factor. Using a gene knockdown approach in neuronal precursor cells and RNA-sequencing, Dr. Herb Lachman (Albert Einstein College of Medicine, USA) reported that ZNF804A appears to affect GABA subtype neurons, genes involved in metabolic syndromes, and genes implicated in nicitine and alcohol dependence. Furthermore, some of the genes affected by ZNF804A may be influenced in an opposite manner depending on the differentiation state of the cell (neural progenitor vs neuron). This bimodal regulation is typical of the Kruppel-like family of Zinc finger transcription factors (such as ZNF804A), which can activate or represses the same gene depending on the presence of other transcription factors.

Functional Consequences of Gene Variants (Reported by Olga Beltcheva and Helen Spiers)

NEWMEDS was presented by the chair as the biggest ever collaboration between Big Pharma and Academia, aiming to develop a translational platform and tools for psychiatric drug development.

Dr. Hrein Stefánsson, deCODE Genetics, talked about "recurrent CNVs affecting fecundity" and presented the findings of the SGENE project. While studying copy number variations recurrently associated with SCZ, the SGENE team noticed that the carriers of some variants had fewer offspring—mutations under negative selection. By focusing only on recurrent, negatively selected CNVs they identify 55 potentially interesting CNV with frequency of less than 1% and tested them for association with SCZ, BP and autism developmental delay. So far they have found an association with one variant—a duplication 10q11.22-23, which is very rare and associated with high risk. Another part of Dr. Stefánsson's work within NEWMEDS is phenotyping population controls that carry CNVs under negative selection with the aim to define a phenotypic stamp of these genetic variants and search which neuronal systems are affected by them. One region of interest is 15q11.2—deletions in this region are associated with selective learning disability. One candidate gene located in this area is the CYFIP1, which has been shown recently to cause fragile X like phenotype in mice [Bozdagi et al., 2012]. At present expression studies are underway as well as fMRFI in the affected subjects for complete elucidation of the effect of 15q11.2 deletion.

Dr. Andreas Meyer-Lindenberg, University of Heidelberg, Mannheim, presented his work on "Gene dosage effects of a CNV associated with SCZ risk on brain structure." Being part of the NEWMEDS Collaboration, he and his group are working on detailed imaging phenotyping of 70 individuals with rare CNV identified by the deCODE Genetics' study described above. Dr. Meyer-Lindenberg argued that due to the mechanism of CNV generation the same chromosomal region could be affected by both deletions and duplications, which in some domains may result in exactly opposite phenotypes. They set out to study these dosage effects of CNV mutations in different brain previously associated with SCZ using Voxel-based morphometry [Radua et al., 2012]. Several brain structures were found to have increased volume in cases with duplications and decreased volume in cases with deletions. Some of these areas are similarly affected in SCZ patients.

Dr. Jacob Nielsen, H. Lundbeck A/S, presented his work entitled "A mouse model of 15q13.3 microdeletion syndrome recapitulates several phenotypes of human syndrome." It is based on a study of the SGENE project discussed above, that identified an association of a microdeletion in 15q13.3 with SCZ). As expected, a downregulation of the six genes located within the CNV was observed in the deletion carriers. No gross abnormalities in the brain were found, which is in agreement with findings in SCZ patients. A marked change in seizure pattern was seen in the transgenic mice, very similar to that described in human with 15q13.3 syndrome [Muhle et al., 2011]. In addition, the CNV carriers were found to have no learning disabilities, but displayed long term memory deficit and higher levels of aggression. Further tests (imaging, in vivo electrophysiology, cognition and heart rhythm) are under way.

Dr. Michelle Rosgaard Birknow, H. Lundbeck A/S, presented "A mouse model of 15q13.3 microdeletion syndrome display preattentive processing deficits and EEG phenotypes seen in SCZ." She described in details the EEG findings of the mouse model introduced by the previous speaker. The goal of the study was to evaluate the specific deficits in the mice and check if they mirror the electro physiological endophentoypes in human SCZ patients. They recorded and analyzed in detail auditory evoked potentials in multiple assays. It was found that the 15q13.3 deficient mice display preattentive processing deficits. The observed EEG phenotypes were found to be similar to those in individuals with psychiatric disorders like SCZ.

Dr. Collins (University of North Carolina) addressed whether miR-137 could contribute to SCZ pathogenesis through regulating cellular pathways. Human neural stem cells (ReNcell-VM) were transduced with vectors to induce over expression or inhibition of miR-137, or control vector. Cells were collected at 24 or 48 hr

post-transduction and RNA sequencing performed using Illumina HiSeq 2000 technology. Genes differentially expressed between cells exposed to control or over expression vector were identified at both time points; at 24 hr, 310 genes were identified, 12% of which were predicted miR-137 targets. At 48 hr, 538 genes were identified, 19% of which were predicted miR-137 targets. Pathway analysis of down-regulated genes revealed an enrichment of cell-cycle genes, consistent with previous findings which have suggested a role of miR-137 in cell cycle regulation. Finally, Dr. Collins found an enrichment of her findings in the results of previous SCZ GWAS, providing further support for an involvement of miR-137 in SCZ pathogenesis.

Dr. Janine Arloth (Max-Planck-Institute of Psychiatry) described data on identifying SNPs associated with changes in gene expression regulated by glucocorticoid (GC) (cis-eQTL analysis). Peripheral blood was used to genotype and measure the gene expression profile of 160 male Caucasians (69 cases, 91 controls) at baseline and 3 hr following stimulation of GC using 1.5 mg dexamethasone. Of a total of 4,395 significant cis-eQTLs, 2,364 significant response eQTLs were identified, >67% of which were located >200 kb from the probe at a mean distance of 406 kb. This was in contrast to baseline eQTLs, which had mean distance of 136 kb, suggesting long-range regulation of gene expression by the glucocorticoid receptor (GR). Additional analysis revealed an enrichment of the GC response element and transcription factor binding sites that modulate GR signaling near eQTL SNPs. Moreover, it was found that response eSNPs were significantly more likely to be associated with MDD than random or baseline eSNPs ($P < 0.001$).

Dr. Lutz Priebel (University of Bonn) investigated the effect of genetic variation on gene expression (expression quantitative trait loci, eQTLs) using a unique sample of 148 pre-mortem human hippocampus samples derived from treatment-resistant epilepsy patients. Whole-genome SNP (Illumina Human660W) and gene expression data (Illumina HumanHT-12v3) was generated, as well as genome-wide methylation data (Illumina HumanMethylation450 array). Dr. Priebel identified 78 trans-regulating eQTLs (defined as >1 Mb between SNP and probe) that withstood multiple testing correction, and 1,925 cis-regulating eQTLs (defined as ≤1 Mb between SNP and probe) that remained significant after permutation-based Westfall-Young correction. Additionally, the analysis investigated the influence of DNA methylation on gene expression, finding that nearly a quarter of eQTLs were also mQTLs. Dr. Priebel hopes to fully integrate the methylation, probe, and transcript data, producing a resource allowing greater annotation of GWAS findings.

To detect cis-acting effects on gene regulation, Dr. Nicholas Bray (King's College London) measured the relative allelic expression of 5 candidate genes in up to 12 brain regions taken from 20 unrelated adult subjects. For every gene, significant differences in allelic expression between brain regions within subjects were found. Elaborating on this finding, Dr. Bray investigated whether allelic expression differences occurred between cell populations, and found ZNF804A displayed significant differences between cells of the CA1 and the dentate gyrus. Adult human brain samples were then used to interrogate the cis-effects of a genome-wide significant risk variant for SCZ (rs1344706) on ZNF804A expression. However, no significant effects were found in any of the brain regions investigated. Conversely, when exploring the effect of this risk variant in fetal brain tissue, it was found to be associated with altered allelic expression from the second trimester. Dr. Bray's work highlights the differing regional, temporal, and cell-specific effects of cis-regulatory variation.

Dr. Douglas Levinson (Stanford University) presented on behalf of Professor Alexander Eckehart Urban and highlighted the concern that there may be an increased rate of de novo CNV formation in induced Pluripotent Stem Cells (iPSCs), potentially altering the utility of this system when studying the genetic basis of psychiatric disease. To address this concern, Professor Urban and colleagues performed whole-genome and RNA sequencing based CNV analysis in fibroblast samples and iPSC lines from two families, finding that on average an iPSC line would have two lineage manifested CNVs (CNVs not found in the fibroblast culture from which the iPSCs were derived). The presence of the same CNVs in the fibroblast tissue of origin was investigated, finding that >50% of the detected LM-CNVs were already present in the fibroblasts, suggesting that de novo CNVs in iPSCs are not necessarily the result of reprogramming. Using whole-genome sequencing is therefore important when using iPSC-models to identify potential genetic confounds.

Dr. Melvin McInnis (University of Michigan) reported on the development and characterization of iPSC lines from controls and phenotypically assessed individuals with BP. Subjects from the Prechter Bipolar longitudinal study with high versus low levels of neuroticism were selected for dermal biopsy. The results presented were produced with 44 iPSC lines (24 of which are from patients with BP) derived from 12 fibroblast stocks taken from five individuals. Testing for microRNA expression differences between iPSC lines derived from controls versus individuals with bipolar revealed approximately 1,000 genes with nominally significant expression differences. Additionally, functional annotation of the iPSC colonies identified an overrepresentation of transcription factors in cell lines from individuals with BP versus controls. These cell lines provide an opportunity to model complex neuropsychiatric illness, and can be used to further characterize the genes which are differentially expressed between bipolar and control cells, particularly at sequential stages of differentiation.

Immunogenetics (Reported by Katri Kantojärvi)

Dr. Bernhard Baune (University of Adelaide) discussed several studies in the field of immune system in emotion and cognitive processing. Immune factors contribute to molecular mechanism of learning, memory, and emotion processing. A contribution of immune genes is highly relevant since observation have been made that cytokines directly interact with molecular mechanisms of memory, learning and neuroplasticity in the hippocampus and the amygdala in particular, both of which are highly relevant to emotion and cognitive processing. In the study of inflammation and emotions IL-1β gene was associated with reduced affective reactivity [Baune et al., 2010]. Several studies have noticed the association between genes of inflammation and cognitive performance. Genetic polymorphisms of cytokines play an important role in cognitive functioning in healthy elderly humans. In a study among

healthy elderly from the general population, the chemokine IL-8 was significantly associated with poor cognitive performance in the memory, attention, and motor domains. In a similar study among healthy elderly individuals, genetic variants of IL-1beta were related to poor memory, whereas a genetic variant of TNF was associated with better cognitive speed performance. In contrast, IL-6 showed no genetic association with cognitive performance in humans so far. Moreover, genetic variants of cytokines may play an important part in predicting anti-depressant treatment response. In different studies, it was shown that the genetic polymorphisms of IL-1beta and IL-11 may play a key role in antidepressant treatment response and emotion processing (IL-1beta) mediated by the amygdala in depression. Immunogenetic research appears to be a promising area for characterizing the predisposition to psychiatric disorder, identifying disease and treatment biomarkers, and developing interventions. Immune factors might be suitable treatment targets in depression and cognitive impairment.

Dr. Bernhard Baune (University of Adelaide) replaced Dr. Udo Dannlowski (University of Marburg) and presented a study of the immune system in neuroimaging. The aim of the study was to clarify whether genetic variation in genes coding for cytokines such as tumor necrosis factor α (TNF-α) or interleukin 6 (IL6) can be linked to neuroimaging markers relevant for depression or other neuropsychiatric disorders. They employed voxel-based morphometry (VBM) in a large sample of well-characterized healthy individuals (N = 303) to analyze the associations between genetic variants of TNF (rs1800629; rs361525), genetic variants of IL-6 (rs1800795; rs1800796, rs2069833, rs2069840) and brain morphology (gray matter concentration). No subject had a life-time history of a psychiatric disorder, auto-immune or chronic inflammatory disorders, chronic infections or any other relevant medical conditions. The findings suggest a neurodegenerative role of the A-alleles of the TNF SNPs rs1800629 (−308G/A) and rs361525 (−238G/A) on hippocampal volumes in healthy individuals. However, a neuroprotective role of the G-allele of the SNP rs1800795 on hippocampal volumes could be discerned. Studies of clinical populations are underway.

Dr. Patricia Zunszain (Centre for the Cellular Basis of Behaviour; King's College London) discussed molecular aspects of the immune system in depression. Depressed patients have higher levels of proinflammatory cytokines, particularly TNF-α, IL-1β, and IL-6. Administration of pro-inflammatory cytokines causes changes in behavior which closely resemble symptoms observed in depression. By using a clinically relevant model of human hippocampal progenitor cells, in this study the effect of cytokines both on the regulation of neurogenesis and on possible neurobiological pathways that are involved in depression were investigated. The cytokine effects on all enzymes involved in the kynurenine pathway was also analyzed. The enzyme indoleamine 2,3-dioxygenase (IDO) appears to be a key player, as it initiates the pathway by degrading tryptophan to produce kynurenine, which can then lead to neurotoxic or neuroprotective products. The differential regulation of these compounds is postulated to explain the behavioral changes experienced by some patients during exposure to inflammatory stimuli. Increasing IDO, IL-1b reduced the availability of tryptophan, the precursor of serotonin. Additionally, it promoted the production of enzymes conducive to toxic metabolites. The detrimental effect of IL-1b on neurogenesis was partially recovered by blocking the neurotoxic pathway. The results suggested that inhibition of the kynurenine pathway may provide a new therapy to revert inflammatory-induced reduction in neurogenesis. Finally, the anti-inflammatory effect of antidepressants from different chemical classes was investigated. Inflammation was induced into the cell model by incubation with IL-1b, and the inflammatory response was quantified by measurement of IL-6 secreted into the supernatant, and also by looking at auto-induction of IL-1b and IL-6 as mRNA. These results add further evidence for the differential anti-inflammatory properties of antidepressants.

Dr. Sarah Cohen-Woods (Institute of Psychiatry, King's College London) discussed childhood stress-reactivity and inflammatory mechanisms in clinical MDD. The stress pathway interacts directly with the inflammatory system, and childhood maltreatment has been consistently associated with depression and with an enhanced inflammatory response. The aim of the study was to investigate if genetic variations in inflammatory genes (*CRP*, *IL-1B*, *IL-6*, *IL-11*, *TNF*, *TNFR1*, and *TNFR2*) interact with environmental exposure to childhood maltreatment to predict risk of developing recurrent MDD. The sample consists of 262 individuals with recurrent moderate to severe MDD (ICD10/DSM-UV), and 288 unaffected individuals screened by questionnaire and telephone interview for absence of psychiatric disorder. The Child Trauma Questionnaire was completed to assess exposure to sexual, physical and emotional abuse, and physical and emotional neglect. DNA was extracted from blood or cheek swabs and genotyped externally using the Illumina Human 610-Quad bead chip, and imputed against the publically available 1,000 genomes data. None of the studied genes showed main effects, although childhood maltreatment was significantly associated with depression. Two genes presented no evidence for interaction (IL1-B, and IL11) while the remaining ones did present some evidence for interaction. The SNP effect occurred in one of two ways—either risk or protection. For genes IL6 and CRP minor allele increased risk of depression in individuals exposed to childhood maltreatment, while the other three were protective. All interaction models tested were additive. This could lead to novel interventions and pharmacological targets; this is particularly salient as a history of childhood maltreatment is also associated with reduced pharmacotherapeutic response.

Comorbidities (Reported by Mariko Brandon)

Preben Bo Mortensen (Aarhus University) focused on observations of four different somatic comorbidities as clues for the etiology of SCZ. The four main comorbidities were cancer, autoimmune disorders, infections, and epilepsy. Patients with psychiatric disorders had a decreased incidence of cancer, but increased morbidity from cancer, which could be the result of decreased access to diagnostic or treatment options. However, the findings should be taken with caution because similar studies have yielded conflicting data. An increase in autoimmune diseases in the schizophrenic population was reported. It was speculated that antibodies that are responsible for the pathophysiology of many autoimmune diseases might also be responsible for the neural degeneration seen in schizophrenics. A direct relationship for increased epilepsy and infections was also seen, with the theory offered that the blood

–brain barrier is decreased with infection, increasing susceptibility to antibodies. Limitations to the work include survivor bias, detection bias in the rates at which cancer and SCZ are diagnosed, and confounding variables such as lifestyle. Although siblings were studied, familial comorbidities were not quite well-established.

Christoph Lang (Harvard School of Public Health) focused on causation and causal interference in genetic epidemiology. Using SNPs, they explored an association between lung cancer and smoking that goes beyond environmental and pathological links? Could there be genes that code for an increased propensity to smoke, in addition to an increased risk of lung cancer? The findings were ultimately found to be inconclusive. A possible explanation was that increased body mass index has been suggested to predispose to nicotine addiction.

Manuel Mattheisen (Harvard Medical School) looked at four asthma phenotypes and causal pathways for depression. However, no obvious gene with a statistically significant correlation was found. The explanations behind the lack of findings were a small sample size (n = 387) and anxiety as a compounding variable. The group next plans to also study the relationship between depression and chronic obstructive pulmonary disease.

Large Existing National and International Datasets and Cohorts (Reported by Vanessa Nieratschker)

Dr. Heike Anderson-Schmidt (University of Göttingen, Germany), described the German Association for Psychiatry and Psychotherapy (DGPPN) Cohort Study. This nationwide initiative will lead to the establishment of a large-scale cohort of 200,000 psychiatric patients and control individuals. In addition to an initial cross-sectional assessment, longitudinal follow-up of the cohort will be performed in order to obtain as much data as possible concerning the course of the various psychiatric disorders. Within the context of this study, the DGPPN aims to establish a national research network, which will both link existing collections of biomaterials and empower centers with well-characterized but small samples. Access to data and samples will be regulated in a transparent manner. Further goals of the DGPPN cohort study are the development and implementation of standard operating procedures and data policies to optimize the quality of biomaterials and data, and the development of a core phenotypic assessment battery. Dr. Anderson-Schmidt pointed out that although the establishment of such standards is not an easy task, its feasibility has been proven in countries in which large longitudinal cohort studies are already in progress, for example, the birth cohort studies in Denmark, Finland, and Norway. The DGPPN cohort has already overcome the major initial challenges of such studies, such as data confidentiality, the integration of data and samples from different sources, and the issue of maintaining the independence of researchers who provide samples and data. Researchers can benefit from the DGPPN cohort for a number of reasons. Firstly, integration of existing data will conform to the highest data protection standards. Secondly, researchers will receive logistic and financial support from the DGPPN in return for contributing to the cohort. Thirdly, researchers will benefit from access to the cohort's large collection of samples and the expertise of other centers. The data and samples will be available for all bona fida psychiatric centers in Germany. During the discussion, the beneficial effect of linking existing biomaterial collections was noted to be a major advantage of the DGPPN cohort study, as individual collections are often too small to answer critical research questions.

Dr. Peter Falkai (University of Munich, Germany) described Brain Net Europe II (BNE), a European-wide association of brain-banks which includes 20 European partners. BNE is an initiative to promote brainbanking, and one of its main goals is to determine the effect of pre- and post-mortem parameters on the preservation of DNA and RNA. BNE aims to set gold standards for brainbanking and to provide training opportunities for researchers. To date, BNE has collected more than 200 brains, including brains from patients with Huntington's disease, AZ, and other psychiatric conditions. The most critical ethical issue with respect to brainbanking is that of informed consent. Discussion is required to clarify whether the consent of the relatives of the deceased to brain removal can be considered adequate. During the discussion, clarification of who is responsible for the samples and who will pay the running costs after the initial funding has ended was requested. Peter Falkai pointed out that these are further issues which have yet to be resolved.

The Norwegian registries, cohorts, and biobanks were described by Ted Reichborn. In Norway, as well as in Denmark, Sweden, Finland, and some other countries, the entire nation is a cohort, as the registries and biobanks cover the majority of the population. In Norway, everyone born since 1964 is included and assessed in 16 mandatory registries. In addition, 19 other clinical registries exist and the number is growing. Some of these registries are linked with a biobank, and biomaterials from 500,000 individuals of all ages (10% of the population) are available. The data derived from each of these registries and biobanks can be linked with data stored in the other Norwegian registries. Since 2002, the Norwegian government has permitted the storage of data without the individual informed consent of the participant. These data are available for research, provided that they are handled in an anonymized manner. Improved techniques present new challenges, for example, the problem of incidental or secondary findings during large sequencing efforts. He pointed out that this particular issue still needs to be addressed and solved.

Dr. Shawn Harmon, discussed the ethical issues surrounding brainbanking in the UK and described existing legal solutions. At the time of writing, the UK has a total of 10 brainbanks. Each is based on a specific disease and was set up for a specific research interest. The legal framework for brain banking in the UK is rudimentary and at present, no specific biobanking regulation exists. The ethico-legal ambitions and objectives are to conduct research in a manner which respects the dignity of the donors, which benefits science, and which strengthens trust in scientists among the general population. Again, the issue of incidental findings and the consequences of scientific uncertainty must be dealt with.

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